Extractable Insulin of Pancreas

CORRELATION WITH PATHOLOGICAL AND CLINICAL FINDINGS IN DIABETIC AND NONDIABETIC CASES

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INTRODUCTION

In discussions of the etiology, course and treatment of diabetes mellitus in man, reference is frequently made to the available data on the relative insulin content of pancreas of the diabetic and nondiabetic organism. Since for human subjects these data have been obtained at widely different periods, with different methods of extraction, and are few in number, a coordinated extension of this field of research is sorely needed. Such a study has been undertaken under the direction of Professor C. H. Best.

The term "insulin content of pancreas" has been widely used. However, there is no proof that the insulin extracted from the pancreas by any method actually represents the total amount of insulin within the pancreas. In fact, with the exception of the group determination of Franklin and Lowell (1949), the published results show an unbroken trend toward progressively higher average levels of insulin extracted from human pancreas. Hence the more accurate expression "insulin extractable from pancreas" will be used to describe the active insulin obtained from pancreas by any stated method of extraction. The possibility that the extractable insulin of pancreas can be represented as a metabolic pool, in or near dynamic equilibrium between production of insulin on the one hand and its release into the blood stream or functional disappearance on the other, has been reviewed by Haist (1944). This concept and the experimental evidence upon which it rests are fundamental to the interpretations of many of the observations made in this paper.

The term "diabetic" describes subjects showing adequate clinical and laboratory evidence of the disease. Conversely, subjects classified as "nondiabetic" will rep-

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resent those for whom there was no clinical or laboratory evidence suggestive of the condition. Subjects who did not show definite presence or absence of diabetes were grouped separately. The term "child" will be used throughout this paper to designate subjects less than 17 years of age who came to autopsy at the Hospital for Sick Children. All others will be referred to as adult subjects.

MATERIALS AND METHODS

The operations preceding the extraction of a pancreas for insulin differed in certain respects for children and for adult subjects. In children, the whole pancreas together with that part of the duodenum to which it was attached was excised at autopsy and stored at -10° C. until it was delivered to the laboratory. After thawing, the pancreatic tissue was carefully dissected away from the duodenum and other adherent tissue, and then weighed. A thin slice from its midsection (body) was placed in Bouin's fixative for histological study, and the balance re-weighed and extracted for insulin. In adult subjects the whole pancreas was weighed in the autopsy room, small sections were removed and fixed for histological study, and the balance delivered for extraction of insulin. At this time it was re-weighed, a visual estimate was made of its fattiness (0 to 4 plus), and a thin slice from the midsection of the body was placed in Bouin's fixative.* Approximately 25 grams of tissue from the body of the pancreas were then weighed out and extracted for insulin. The method of Scott and Fisher (1938) for insulin extraction was employed in all cases.

Estimations of the concentration of insulin in such extracts were made, using a mouse-convulsion method of assay meeting all of the requirements recommended for such assays by Bliss (1950). In a few cases where the insulin concentrations were too low to cause convulsions in mice, a mouse blood sugar method for insulin assay was employed (Wrenshall, Collins-Williams and Hartroft, 1949).

The known dilution factors and weight of pancreas extracted provided the additional information required for the calculation of the concentration of extractable insulin was calculated for each whole pancreas, per kilopancreas). In addition, the total amount of extractable insulin was calculated for each whole pancreas per kilogram of body weight, per inch of body height, and per square meter of body surface at death. Figures for body surface area were obtained from a nomogram, prepared by Boothby and Sandiford,† for adult subjects. A nomogram designed by Hannon‡ from the data of DuBois (1936) was used in the estimation of body surface area in children.

Employing the above procedures, the extractable insulin of the pancreas at autopsy has been determined and related to the clinical and pathological data collected for 213 human subjects. Of these 139 were nondiabetic, 68 of whom were less than 10 years of age at death. Of the remainder, 64 were diabetics and 10 were possible diabetics. These 10 were placed in an unclassified group since the diagnosis of diabetes mellitus was not definitely established.

A summary of the published data on the insulin extracted from the pancreases of diabetic and nondiabetic human subjects is shown in Table 1. There is no significant difference in magnitude (by "t" test at the 5 per cent level, or even at the 50 per cent level) between the average number of units of extractable insulin per pancreas in the nondiabetic subjects of Scott and Fisher (1938) and their counterparts in the present series. For this reason, and with the permission of these authors, their data have been combined with our own in Figure 6 in order to provide a larger group.

TABLE 1 Available data on the insulin extracted from human pancreas at autopsy for adult diabetic subjects (D.) relative to adult nondiabetic controls (N.D.)

Source of Data and Type of Subject		No. of Subjects	Av. Age (years)	Insulin Extracted from Pancreas: Units/Gm. of Pancreas Av.±S.E.	Insulin Extracted from Pancreas: Units/Pancreas Av.±S.E.
Pollak (1926)	D.	9	53	0.08*	—
	N.D.	4	55	0.24±0.01	—
Scott & Fisher (1938)					
Hospitalized Sudden death	D.	14	62	0.47*	46*
	N.D.	10	52	1.6 ± 0.3	189±26
Present Series					
Hospitalized	D.	57	64	1.02*	77*
Hospitalized Sudden death	N.D.	52	54	2.37±0.14	203±12
	N.D.	9	62	2.14±0.15	178±18

*No standard error is stated for this group as the frequency distribution is not a normal one.

*A report on the histology of the pancreas for a majority of the adult subjects for whom data are presented in this paper has been published by Hartroft (1950).

†A reproduction of this nomogram is found in the text by E. F. DuBois entitled Basal Metabolism in Health and Disease, 3rd ed., Philadelphia, Lea and Febiger, 1936.

‡Ibid.

RESULTS AND DISCUSSION

1. *Effects of Uncontrollable Variables*

In the hospitalized adult nondiabetic subjects there was no correlation between the concentration of extractable insulin of pancreas (I) and either hours postmortem at autopsy (H) or days of confinement to bed preceding death (D). Similarly, there was no correlation between either H or D and the amount of extractable insulin per square meter of body surface (M), during the time intervals covered by these data (Figure 1).‡ The less detailed analysis of Figure 2 shows a similar lack of correlation between the concentration of extractable insulin of pancreas and the hours postmortem at autopsy for the nondiabetic children studied.

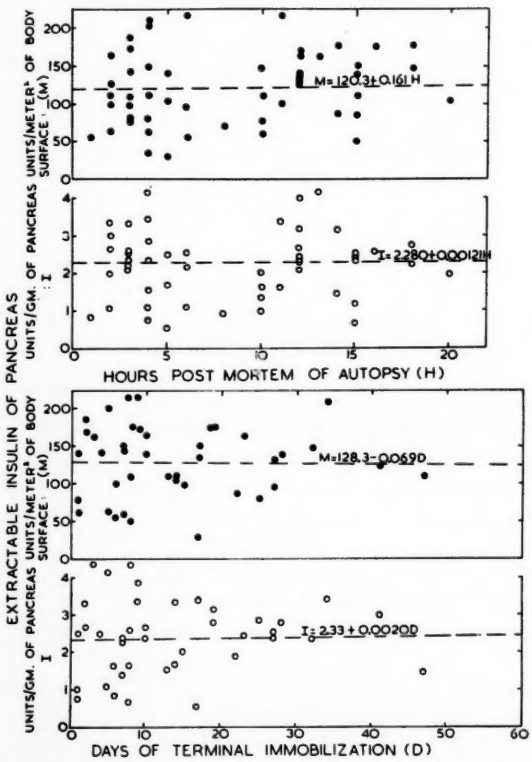

FIGURE 1 Effects of the uncontrolled factors hours p.m. of autopsy (H) and days of confinement to bed preceding death (D) on the concentration of extractable insulin of pancreas at autopsy in adult nondiabetic humans

A comparison of the average amounts of insulin extractable from pancreas at autopsy in nondiabetic adult subjects following periods of terminal hospitalization or sudden death is made in the second half of Table 2. It is found that units of extractable insulin per kilogram of body weight and per square meter of body surface are significantly higher in the hospitalized than in the sudden death group. Units of extractable insulin per gram of pancreas, per pancreas and per inch of body height show differences in the same sense but of low statistical significance. The above situation would arise if, in the average nondiabetic subject, body weight were lost during terminal hospitalization without reduction in the extractable insulin of pancreas.

Mirsky (1945) has suggested that the insulin extractable from pancreas in hospitalized subjects might differ appreciably from that in subjects after sudden death. The analyses presented in Figure 1 and Table 2 and discussed above indicate that if such a difference exists it is small. Neither of the conclusions reached by Franklin and Lowell (1949) concerning the lowering effects of postmortem change or hospitalization on the insulin extractable from human pancreas at autopsy receives any support from our data.

2. *Sex Differences*

The five available units for the extractable insulin of pancreas in hospitalized nondiabetic adult subjects have been examined for sex differences in the first half of Table 2. The only difference between the averages for each sex having any statistical significance was that for units of extractable insulin per whole pancreas ($p = 0.13$). These observations indicate that the amount of insulin extractable per pancreas increases in direct proportion with body size, and that the sex difference in units of insulin per whole pancreas is a result of the characteristic sex difference in body size.

3. *The Insulin Extractable from Different Regions of the Human Pancreas*

The extractable insulin from different portions of the human pancreas was determined in one nondiabetic eight-year-old child and six adult human subjects, one of whom was diabetic. The child's pancreas was cut into two approximately equal parts describable as the attached duodenal (head-) and free splenic (tail-) halves. For each of the adult subjects the pancreas was

‡The following equations of linear regression were obtained by the method of least squares for the data of Figure 1:

$$I = 2.28 + 0.0012H$$
$$I = 2.33 + 0.0020D$$
$$M = 120.3 + 0.161H$$
$$M = 128.3 - 0.069D$$

TABLE 2 Average values for the extractable insulin of pancreas, expressed in terms of five units for adult nondiabetic subjects. The effects of terminal immobilization and of sex on these units are indicated in statistical terms

	Extractable Insulin of Pancreas				
	Units/Gm. of Pancreas	Units/ Pancreas	Units/Kg. of Body Weight	Units/Inch of Body Height	Units/Sq. Meter of Body Surface
35 Hospitalized + Sudden Death Male subjects (av. age: 56 yrs.) Average ± St. error	2.32±0.15	216±14	3.50±0.23	3.22±0.21	127±8
St. deviation x 100 / average	39.3%	37.8%	39.4%	38.0%	38.4%
23 Hospitalized + Sudden Death Female subjects (av. age: 54 yrs.) Average ± St. error	2.29±0.22	183±17	3.37±0.31	2.99±0.30	120±11
St. deviation x 100 / average	46.4%	45.1%	44.1%	47.4%	44.6%
p for difference between averages*	>0.5	0.13	>0.5	>0.5	>0.5
50 Hospitalized subjects: (av. age: 56 yrs.) Average ± St. error	2.25±0.15	210±12	3.58±0.21	3.21±0.19	128±7
St. deviation x 100 / average	46.1%	40.4%	41.2%	41.2%	40.6%
11 Sudden Death subjects: (av. age: 66 yrs.) Average ± St. error	2.04±0.13	174±20	2.60±0.24	2.70±0.30	101±10
St. deviation x 100 / average	18.0%	31.6%	26.1%	31.6%	27.3%
p for difference between averages*	0.28	0.18	0.02	0.18	0.06

*Probabilities (p) that differences between averages are not statistically significant were interpolated from t tables.

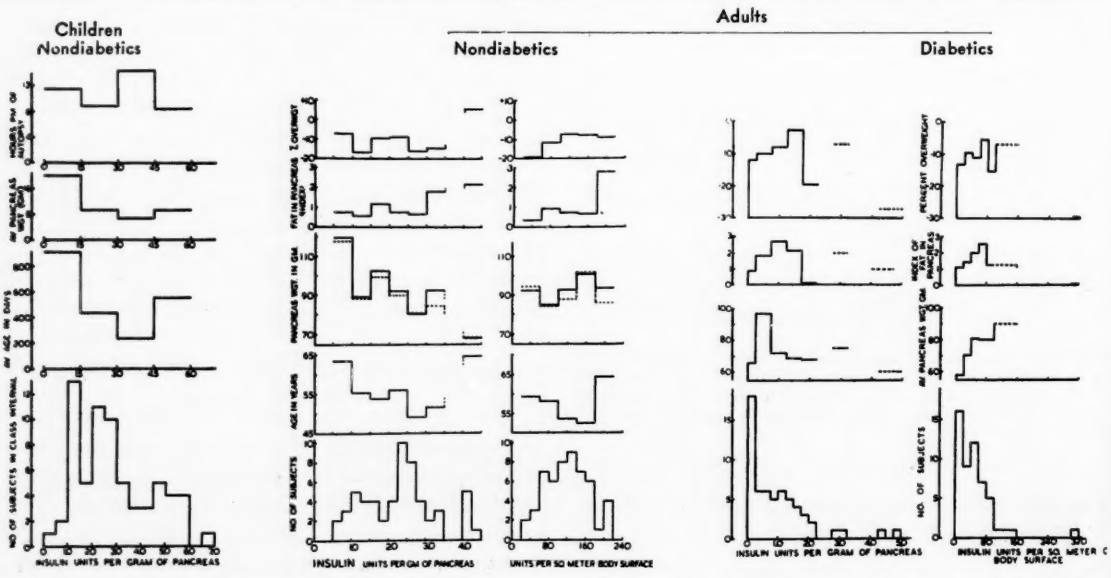

FIGURE 2 Frequency distributions for the extractable insulin of human pancreas, and variations in body characteristics with it

subdivided into three approximately equal parts, representing the head, body and tail.

The concentration of extractable insulin in the tail half of the child's pancreas was 1.9 times as high as in the head portion. Taking the average concentration of extractable insulin in the head of the pancreas as 1.00, the average concentrations of extractable insulin in the body and tail portions of the adult nondiabetic pancreases were 1.30 and 1.67, respectively. The concentration of extractable insulin in the tail of the pancreas of the adult patient with diabetes mellitus also exceeded that in the head. In this single instance the concentration in the tail of the pancreas was 2.08 times that in the head.

The above results are comparable to a study made on the pancreas of the dog (Bell, Best and Haist, 1942). They are supported by the histological finding that islet tissue is more abundant in the tail than in other regions of the pancreas. These findings suggest that when it is impractical to extract the entire pancreas, a specimen from the central portion should be chosen.

4. Concentration of the Extractable Insulin of Pancreas in Islet Tissue. *

By means of the islet cell volume estimations made by Ogilvie (1937) on nondiabetic human subjects at autopsy and the data on the concentration of extractable insulin of the pancreas in nondiabetic subjects of similar ages in the present series, estimates have been made of the number of units of extractable insulin per gram of islet tissue. The subjects have been subdivided into four age groups (10—100, 101—1,000, 1,001—10,000 and 10,001—100,000 days at age of death) and the average values for units of extractable insulin per gram of islet tissue for each age group have been plotted as a function of age (Figure 3).

Employing histological methods, Gomori (1941) has estimated that the beta- to alpha-cell frequency ratio in the islets of Langerhans of nondiabetic adult human subjects varies from 3/4 to 8/9. Using the average value for this ratio, an average value of 150 units of extractable insulin per gram of islet tissue for adult nondiabetic human beings (Figure 3), and assuming that about 20 per cent of the islet volume is occupied by other materials than alpha- plus beta-cells, then the average concentration of extractable insulin in the beta-cells would amount to approximately 220 units per gram

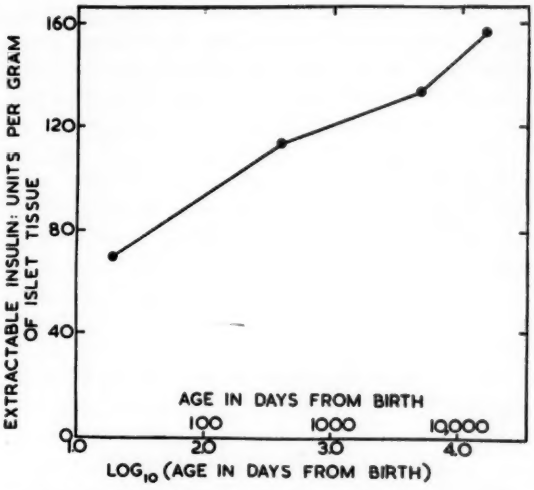

FIGURE 3 Trend with age in the extractable insulin of pancreas per gram of islet tissue in nondiabetic human subjects at autopsy. Based on islet weight determinations of Ogilvie, 1937, and extractable insulin determinations of the present series

of beta-cell tissue. Barring gross error in its measurement, the extractable insulin of pancreas cannot be an overestimate of the insulin content of pancreas. Therefore, providing that the extractable insulin of pancreas is largely contained in the beta-cells, it follows that at least 1 per cent of the wet weight of these cells at autopsy is composed of insulin.†

The recently published data of Bornstein (1951) indicate that the insulin content of normal human blood is about 0.1 milliunits per milliliter during fasting. This amounts to approximately 5×10^{-7} of the average concentration of the extractable insulin estimated for the beta-cells. Therefore, it might be expected that the release of insulin from the islets of Langerhans into the blood stream could be explained on the basis of a high diffusion gradient. However, the experiments of Anderson and Long (1947) indicate that such an explanation may be insufficient since, in their experiments, even prolonged perfusion of rat pancreas with rat blood caused no increase in its concentration of insulin unless the perfusing blood contained more than the normal concentration of dextrose. This suggests that an increase in the concentration of blood sugar acts in some way upon the insulin-containing cells to permit

* See Section 11 for new and direct evidence that insulin in the human pancreas is located only in the islets of Langerhans.

† Even if no assumption were made concerning the distribution of extractable insulin throughout the islet volume, its concentration in the islet volume would still be of the order of 1 per cent of the wet weight of islet tissue.

an increased outflow of insulin into the blood. The transfer probably is then accomplished by diffusion which is facilitated by the large concentration gradient. However, our speculation must await confirmation and extension of the findings before it assumes significance.

The figures reported by Gomori (1941) and the histological observations made in the present series indicate that the proportion of beta- to alpha-cells in the islets of Langerhans of nondiabetic human subjects increases between birth and maturity. Since the beta-cells are believed to represent the source of insulin in the pancreas, this change in the proportion of cell types may represent the principal cause of the observed increase with age in the concentration of extractable insulin of islet tissue seen in Figure 3.

5. *Age Trends in Nondiabetic Subjects*

Variations in the extractable insulin of the pancreas for nondiabetic subjects with age at death are illustrated in Figure 4, in which individual results are expressed as units of insulin per whole pancreas, per gram of pancreas and per inch of body height. While the use of logarithmic units* illustrates age trends to advantage for young subjects, those for adult subjects are seen more clearly in Figure 5, in which a linear time scale is employed.

The levels of extractable insulin in premature infants are found to be below the average values in infants born at full term.† The extractable insulin of the pancreas in non-premature infants appears to pass through a maximum at about six months after birth, followed by a shallow minimum at about three years of age when expressed in terms of units per pancreas and per inch of body height (Figure 4). There is a poorly defined downward trend in the concentration of extractable insulin (units per gram of pancreas) during this time. After the third year of life, the extractable insulin of pancreas per inch of body height and per pancreas rise continuously, reaching the adult levels between the twelfth and seventeenth years of life.

Values for units of extractable insulin of pancreas per kilogram of body weight and per square meter of body surface could not be estimated for most of the children included in this series because of lack of the requisite data on body weights at autopsy. However, approximate values for 28 subjects were obtained from measurements made in the wards five days or less before death. It was observed that, within the first year of life, the extractable insulin of pancreas expressed in terms of these two units reaches or exceeds the average values for adult subjects. In achieving these values those present at birth are doubled by the end of the first year.

If constancy with age be taken to represent a desirable feature in a unit for the extractable insulin of

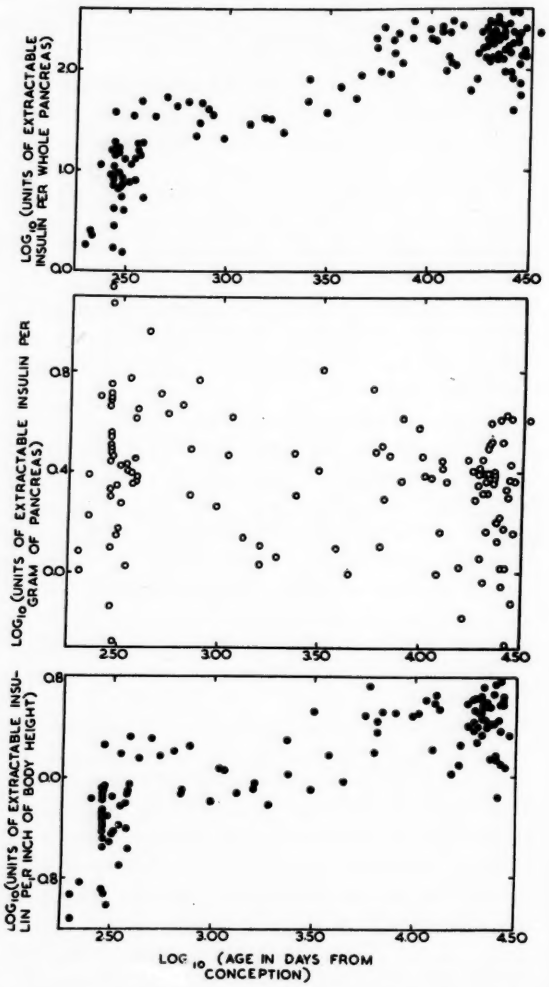

FIGURE 4 Variations in the insulin extractable from pancreas at autopsy with age at death in nondiabetic human subjects. Logarithmic scales are employed to bring out variations occurring during growth

* Both logarithmic and linear age scales are shown in Figure 3 to illustrate how they are related.

† The $\log_{10}$ (age in days from conception) at full term is taken as 2.45 in Figure 4, representing the logarithm of 285 days.

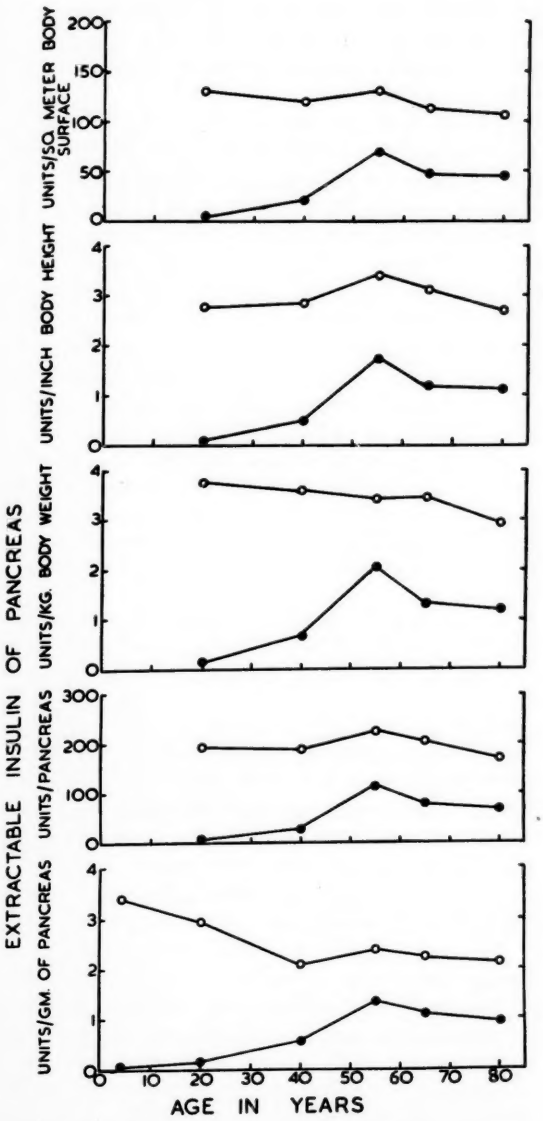

FIGURE 5 Age trends in the extractable insulin of human pancreas at autopsy for diabetic (●) and nondiabetic (o) subjects expressed in terms of five units. Age trends in subjects below 10 years of age are illustrated elsewhere

the pancreas, then units of insulin per gram of pancreas, per square meter of body surface and per kilogram of body weight are favored over the units per pancreas and per inch of body height. Units of insulin per gram of pancreas is the simplest figure to determine and is least subject to errors of measurement. The extractable insulin of the pancreas per square meter of body surface is probably more directly related to the total metabolism of the body than are any of the four other available units.

Following the first two decades of life, there is evidence of a gradual downward trend in the extractable insulin of the pancreas in nondiabetic humans when expressed as units per gram of pancreas, per whole pancreas, per kilogram of body weight and per square meter of body surface, but not when expressed as units per inch of body height (Figure 5). The trend is interrupted by a shallow maximum reached in four of the five graphs of Figure 5 in the fifth decade of life. The maximum is most prominent when units of extractable insulin per inch of body height are plotted, and is absent when the results are expressed in terms of units of insulin per kilogram of body weight .

The first maximum in the extractable insulin of the pancreas, which occurs at about six months after birth, falls within the period during which weaning of infants usually occurs. It may, therefore, be associated with metabolic readjustments to qualitative or quantitative change in the intake of food, or both, which take place at this time. The fact that the total number of units of extractable insulin per pancreas in adolescent subjects is as great or greater than in adults is not surprising if the extractable insulin of the pancreas is a positive function of intake of food. The average caloric requirement of children fourteen years of age and over is as large or larger than of adults of the same sex (Holt and Fales, 1921).

Trends in the extractable insulin of the pancreas occurring in hospitalized nondiabetic subjects after the second decade of life will be considered under Section 9 in relation to the diabetic subjects for which they served as controls.

6. *Biological Variation and Errors of Measurement in Relation to the Extractable Insulin of Pancreas*

Average values for the extractable insulin of pancreas and their per cent standard deviations have been calculated in terms of five different units for adult nondiabetic subjects (Table 2). Frequency distributions of values for the extractable insulin of pancreas expressed as units per gram of pancreas and per square meter of body surface are compared in Figure 2 for adult subjects, and for units per gram of pancreas for children.

The theory of errors predicts that the contribution of errors *of measurement* to the per cent standard deviation of the five units for extractable insulin of pan-

creas used in this paper will be smallest when this variable is expressed as units per gram of pancreas, larger when units per pancreas is used, and largest when expressed as units per square meter of body surface. Contributions of errors of measurement to the per cent standard deviations of the other two units will be intermediate between those of the last two mentioned above. This prediction can be made since the per cent standard deviation of a product or quotient corresponds in magnitude with the sum of the per cent standard deviations of the individual factors entering into the product or quotient.

It is, therefore, of interest to find little or no evidence of such differences in standard deviation among the five units investigated, the average standard deviation value being about ± 40 per cent in each case (Table 2). This situation would arise if the principal factor producing the dispersion in values for the extractable insulin of pancreas had its origin in the human subjects rather than the experimental measurements. The per cent standard deviation in the ratio of islet to acinar-plus-islet mass in adult human subjects was calculated from the data of Ogilvie (1937) and found to be ± 42 per cent. If islet mass per gram of pancreas in adult human subjects is taken as an approximate index of the amount of insulin per gram of pancreas, then the close agreement between the above two standard deviations provides substantial confirmation for the belief that biological variation rather than inaccuracies in measurements constitutes the principal cause of the observed standard deviation.*

7. *Pancreas Size and Concentration of Extractable Insulin*

A well-marked inverse variation in concentration of extractable insulin with total weight of pancreas appears by inspection to exist for adult nondiabetic subjects. This variation is no longer evident when units of extractable insulin per square meter of body surface are compared with pancreas weight (Figure 2),† which indicates the relatively greater value of the latter unit over the former for use in relation to the total metabolism of the body.

In those adult nondiabetic subjects for which the number of units of extractable insulin per gram of pancreas is high and the weight of pancreas small, the extractable insulin per square meter of body surface is also high in relation to the average for the entire group of nondiabetic adults. These subjects were characteristically overweight at death, and their pancreases were charged with fat (Figure 2). This means that the number of units of extractable insulin per gram of fat-free pancreas is even higher than the data presented in Figure 2 indicate. In one subject, 65.9 per cent of the wet weight of the pancreas consisted of fat, and the extractable insulin of pancreas amounted to 8.0 units per gram of fat-free pancreas. This suggests a very high rate of production and release of pancreatic insulin. This situation is of great interest in view of the frequency with which obese subjects develop diabetes.

8. *The Extractable Insulin of Pancreas in Nondiabetic Subjects Compared with Assigned Cause of Death, and Unusual Conditions of Carbohydrate Metabolism*

The average extractable insulin of pancreas at autopsy associated with different causes of death in nondiabetic adult subjects is shown in the first half of Table 3. None of these average values differs significantly at the 5 per cent level from the corresponding average figure for the nondiabetic adult group after sudden death.

The two most obese nondiabetic subjects of the present series, both females, were 36 and 39 per cent overweight at death.‡ Both deaths resulted from heart disease. The average values for the extractable insulin of pancreas in these subjects were 3.28 units per gram of pancreas, 238 units per pancreas and 133 units per square meter of body surface, all of which are higher than the average for the nondiabetic female subjects of

* An example will illustrate the masking effect of a large source of variation over a smaller one: If the standard deviation produced by biological variation alone in the extractable insulin of pancreas amounted to ± 40 per cent while that produced by inaccuracies of measurement amounted to ± 15 per cent, the resultant or total standard deviation would amount to only $\sqrt{40^2 + 15^2} = \pm 42.7$ per cent. On the basis of independent analyses we estimate that the combined inaccuracies involved in the measurement of the extractable insulin per gram of pancreas are representable by a standard deviation of less than ± 15 per cent.

† The broken lines in this figure are values for pancreas size corrected for differences in sex distribution; the full lines represent the uncorrected data.

‡ Standard values for the calculation of percentages of overweight and underweight were taken from the Medico-Actuarial Mortality Investigation, vol. 1, New York, 1913. Standard subjects of the 1912 series were weighed while wearing "usual indoor clothing" with shoes removed. The subjects included in the current series whose weights are compared with such standards were weighed at autopsy without clothing. It is, therefore, clear that all of the percentage overweight figures cited above will be too low.

Table 2. At the other extreme, the two most emaciated nondiabetic subjects of the present series, also both females, were 48 and 49 percent underweight. The average values for the extractable insulin of pancreas in these subjects were 0.92 units per gram of pancreas, 70 units per pancreas and 69 units per square meter of body surface. Thus the extremes of overweight and underweight in this small series of human subjects have been found to be associated with high and low levels of the extractable insulin of pancreas, respectively. However, in subjects of the series with less extreme degrees of overweight and underweight at death, no characteristic differences from the average values for the extractable insulin of pancreas were observed.

One adult female subject of the present series with marked hypoproteinemia and anasarca resulting from starvation of psychogenic origin had a body weight 34 per cent below standard. The extractable insulin of pancreas was extremely low (1.08 units per gram of pancreas, 43 units per pancreas and 33 units per square meter of body surface). Two children of the present series could not ingest adequate food from birth due to congenital anomalies, and died after three and fifteen weeks of undernutrition of sufficient degree to retard or prevent growth. The extractable insulin of pancreas was at the lower extreme of the normal range in the former case, and even lower in the latter at death.

While it is difficult to estimate the statistical significance of the above depressions of the extractable insulin of pancreas, their agreement with the findings from controlled experiments on undernutrition with animals is good (Best, Haist and Ridout, 1939; Haist,

TABLE 3 Extractable insulin of pancreas at autopsy for deaths resulting from different conditions in diabetic adult subjects and their nondiabetic controls. (Average values without subdivision as to cause of death are also included for adult subjects not classified as diabetic or nondiabetic)

Cause of Death	No. and Sex of Subject	Av. Age at Death (years)	Average Pancreas Weight (gm.)	Extractable Insulin of Pancreas		
				U/gm. of Pancreas	U/Pancreas	U/(Meter)^2 Body Surface
Nondiabetics						
Chronic heart disease	9M 3F	55	104	2.49	248	150
Acute heart disease	2M 3F	63	83	3.32	261	164
Hemorrhage (cerebral, G.I., etc.)	5M 2F	63	83	2.46	191	120
Malignancy	6M 3F	53	80	2.58	200	130
Infection	10M 3F	57	88	2.32	193	107
Vascular occlusion (excluding coronary arteries)	2F	75	90	1.55	132	97
Liver disease	1M	17	60	3.32	199	110
Miscellaneous	4M 5F	44	94	2.23	207	109
Diabetics						
Chronic heart disease	3M 11F	63	68	1.31	79	52
Acute heart disease	3M 3F	62	116	0.64	76	43
Hemorrhage (cerebral, G.I., etc.)	5M	55	83	0.23	26	15
Malignancy	5M 2F	62	72	1.41	114	72
Infection	5M 9F	66	79	1.09	85	62
Vascular occlusion (excluding coronary arteries)	1M 3F	68	74	1.06	62	33
Liver disease	2M 1F	61	92	0.88	76	46
Miscellaneous	4M 5F	56	64	0.97	69	43
Not classified as diabetic or nondiabetic	3M 7F	61	86	1.44	125	68

1944). The opposite effect, noted above in the two adult subjects with the greatest degrees of overweight, may reasonably be considered to correspond with the effects of overnutrition.

The concentrations of extractable insulin were measured in sections of pancreas removed from a series of six living subjects suffering from unexplained hypoglycemia. Histological studies revealed no definite structural evidence of disease. In some cases, portions of the pancreas were removed at successive operations and in such cases only the average values for all removals is considered here. Of the six values, only one (5.0 units per gram of pancreas) exceeded the average for nondiabetic subjects of similar age. The remaining five values ranged between 0.60 and 1.70 units of extractable insulin per gram of pancreas.

One child dying with glycogen-storage disease was included in the present series. The extractable insulin of pancreas fell in the lower part of the range of values for nondiabetics of corresponding age for each of the three units shown in Figure 4. Since glycogen-storage disease in children is characterized by a degree of hypoglycemia, the lowered value found for the extractable insulin of pancreas might be associated with this circumstance. This speculation might also be extended to the subjects with unexplained hypoglycemia where a similar association is observed.

Two infants of the series were born of diabetic mothers. In one subject, delivered 7.5 weeks before term, and weighing 5 pounds and 12 ounces, the heart was twice the normal weight and the islets of Langerhans were numerous and large. The extractable insulin of pancreas was above the trend values for the three available units of Figure 4, but in each case fell within the region of scatter covered by the other values for nondiabetic subjects of corresponding age. The second subject, born at full term and weighing 4 pounds and 7 ounces, had an extractable insulin of pancreas which fell within the range for nondiabetics dying at the same age (4 days after birth).

Among the nondiabetic adult subjects were two of particular clinical interest. One showed considerable interstitial fibrosis of the pancreas with marked reduction of islet tissue. In the other there was hyalinization of many of the islets of Langerhans. The concentrations of extractable insulin in these pancreases amounted to 0.52 and 0.82 units per gram of pancreas, respectively, which represents 23 per cent and 36 per cent of the average for adult nondiabetic subjects. Although laboratory investigation was limited, in neither patient was there clinical evidence of diabetes mellitus.

9. *Comparability of Diabetic Subjects and Their Nondiabetic Controls: Body Characteristics and Extractable Insulin of Pancreas*

The hospitalized nondiabetic adult subjects of the series represent the controls for the adult diabetic patients. They correspond with the diabetic group in sex and age distribution, and in assigned causes of death (Table 3). Diabetic and nondiabetic subjects were entered into the series in random order.

Since the weight of the body was used in establishing one of the units for the extractable insulin of pancreas, it was advisable to determine the combined effects of terminal illness and death upon the body weight at autopsy. Wherever hospital values for the weight of adult subjects during the last year of life (X) were available, these were compared with the corresponding weights taken at autopsy (Y). Straight lines of best fit were determined separately for diabetic and nondiabetic subjects, using the method of least squares. The equations of linear regression are as follows:

$Y = 2.79 + 0.871X$ kilograms for diabetic subjects

$Y = 0.87 + 0.864X$ kilograms for the nondiabetic controls

Average body characteristics and duration of terminal immobilization in the adult diabetic patients and their controls are contrasted in Table 4.

The slopes of the straight lines of best fit, the equations of which are stated above, differ by less than 1 per cent, and the lines pass close to but not through the origin. Hence, insofar as terminal changes in body weight are concerned, the nondiabetic controls are closely comparable with the diabetic patients, and the weight of the body at autopsy represents a reliable index of body weight before onset of terminal illness. The height of the body was found to show no statistically significant difference in diabetic and nondiabetic adult subjects of either sex at any age.*

It is consistently found in Table 3 that the average extractable insulin of pancreas in adult diabetic subjects whose death resulted from one of the listed conditions is lower than the average value for the corresponding nondiabetic group. Thus the coexistence of the diabetic condition is found to represent the prin-

*Average values and their standard errors of estimate for body height in adult subjects of the present series are as follows:

Nondiabetic adult males	(31):	67.0 ± 0.49 inches
Diabetic adult males	(24):	66.5 ± 0.67 inches
Nondiabetic adult females	(18):	61.5 ± 0.62 inches
Diabetic adult females	(22):	62.0 ± 0.36 inches

TABLE 4 Average body characteristics and duration of terminal immobilization in the adult diabetic subjects and their nondiabetic controls

Factor Compared	Diabetics		Nondiabetics	
	No. of Subjects	Average Value	No. of Subjects	Average Value
Terminal Illness				
Days at home (approx.)	44	15.5	39	34.0
Days in hospital	60	20.0	44	11.3
Hours p.m. of autopsy	58	8.5	54	8.7
Age at diabetes diagnosis (yrs.)	55	53.3		
Age at death (yrs.)	60	61.5	56	54.0
Body weight at autopsy (kg.)	57	59.0	53	59.1
Pancreas weight (gm.)	60	76.2	56	97.5
Liver weight (gm.)	61	1625	56	1510
Heart weight (gm.)	61	400	54	419
Two kidney weight (gm.)	60	356	55	297
Pituitary weight (gm.)	35	0.5	37	0.5
Thyroid weight (gm.)	48	36.4	40	23.6

cipal pathological factor associated with depression of the extractable insulin of pancreas in adult human beings, although in no sub-group of Table 3 can the average depression be described as profound.

While, as a general rule, there is a moderate downward trend with advancing age in the extractable insulin of pancreas of the control group, the opposite is observed in the diabetic group below the fifth decade of life. Above this age the trend for diabetic patients parallels that for the control group (Figure 5). Both diabetic patients and control patients pass through a peak in the fifth decade of life for all five units with one exception—the trend with age in units of extractable insulin per kilogram of body weight in nondiabetic subjects.

The heights of individuals in both the diabetic and nondiabetic groups of adult subjects were found to be closely comparable and showed no age maximum or minimum. Therefore, it may be concluded that the maximal values in the fifth decade of life for units of extractable insulin per inch of body length were caused by an increase in the average extractable insulin of pancreas at this age. The lack of a corresponding rise in the extractable insulin per kilogram of body weight in this decade in the nondiabetic group must then reflect the presence of a maximal value in average body weight in these subjects at or near this time. The coincidence of maxima in averages for both body weight and extractable insulin of pancreas in the nondiabetic control group is in accord with the well-supported view that the requirement for insulin is increased by an increase in body weight.

10. Extractable Insulin of Pancreas in Diabetic Coma

Data concerning the nine diabetic patients who died as a result of diabetic coma are shown in Table 5. With the exception of one patient, diagnosed clinically as being insulin-resistant during his terminal illness, the subjects of this group are characterized by their very low concentrations of extractable insulin at autopsy and

TABLE 5 Extractable insulin of pancreas in subjects dying within one day of showing a CO_2-combining power of 20 vols. per cent or less (diabetic coma)*

Autopsy No.	Sex	Age in Years		Known Duration of Diab. (years)	CO_2C.P. (vols. %)	Pancreas Weight (gm.)	Extractable Insulin of Pancreas	
		At Diab. Diagnosis	At Death				u/gm.	u/panc.
HSC 129/49	M	2	2	0	12	25	<0.1	<2.
HSC 73/51	M	7	7	0	19	22	0.07	1.5
HSC 292/50	F	13	13	0	10	32	0.11	3.5
TGH 73/51	F	15	18	2.8	14	50	0.24	12.0
TGH 225/50	M	41	49	8	20	33	0.05	1.6
TGH 161/46	M	48	56	8	15	40	0.01	0.3
StM 182/49†	M	56	66	11	13	150	0.82	123
TGH 103/49	M	46	69	23	10	40	0.05	2.0
TGH 28/48	M	58	78	20	18	30	0.08	2.4

*Joslin, Root, White, Marble and Bailey: Treatment of Diabetes Mellitus, 1946, p. 420.
†Previously reported before the Toronto Diabetes Association by Dr. W. E. Hall as an insulin resistant subject during terminal illness.

by the small size of the pancreas. In the insulin-resistant subject, the pancreas was above average in weight and contained a relatively large amount of extractable insulin which, however, was still less than that of the average nondiabetic adult. While the observations in eight of these patients support the widely accepted view that diabetic coma represents the end-result of profound insulin insufficiency, the findings in the insulin-resistant patient suggest that there was failure either of liberation or of action of insulin, or of both. Since this latter patient received large doses of insulin, it is obvious that there was a failure of the action of insulin.

11. Histology and Extractable Insulin of Pancreas in Diabetic Human Subjects and in Experimental Diabetic Animals

Of the five histological classifications of the diabetic pancreas made by Hartroft (1950) for adult subjects of this series, one group was characterized by pronounced loss of islet tissue. The average extractable insulin of pancreas of the subjects of this group amounted to less than 3 per cent of the average for nondiabetic controls. In contrast, averages of from 47 to 60 per cent of the control values were found in the other four histological classifications which did not show pronounced loss of islet tissue, including beta-cells. This provides further direct experimental support for the generally accepted view that the islets of Langerhans represent the source of insulin in the human pancreas.

Data concerning the insulin which could be extracted from the pancreas in various types of experimental diabetes in animals have been collected from the literature wherever values in nondiabetic controls have likewise been determined and stated.* These are expressed as units of insulin per pancreas for diabetic rats and per gram of pancreas for dogs, and are contrasted in Figure 7 with similarly expressed results for the diabetic patients of the present series. The dotted lines in the distribution for partially depancreatized dogs represent values expressed as units of insulin per gram of pancreas. These would have to be moved down to approximately one-eighth of the values shown if expressed as units per pancreatic remnant.

The pattern of distribution of individual values for units of insulin extracted from pancreas in animals with experimental diabetes is quantitatively different

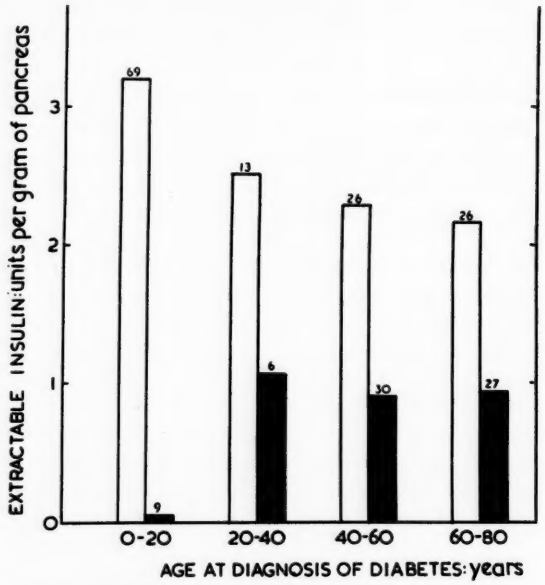

FIGURE 6 Variation in the average extractable insulin of human pancreas at autopsy in diabetics (black strips) with age at diagnosis of diabetes. Values for nondiabetic controls at death are shown as white strips. The number of subjects in each group is shown above the strip

from that for the full series of diabetic human subjects of the 1944-51 group with which it is compared in Figure 7. All but one of the 22 values in the distribution for animals with experimental diabetes falls well below one-tenth of the average value for the corresponding nondiabetic controls, while 40 of the 58 human subjects lie above this level.

The reason for choosing the 10 per cent level as a reference in the above comparison is that it is approximately equal to the fraction of functioning pancreas which is just sufficient, after partial pancreatectomy, to maintain the fasting blood sugar within the normal range in dogs (Allen, 1913), mice (Pauls and Bancroft, 1950), rats (Foglia, 1944), or in alloxan-treated rats (Wrenshall, Collins-Williams and Hartroft, 1949). The minimum amount of pancreas which can perform this function in individual cases will, of course, be affected by the activity of antagonistic hormones and other factors.

Permanent changes in the islet cells in animals with experimentally induced meta-diabetes have been frequently described in the literature as conspicuous atrophy of the islets of Langerhans with islet remnants consisting chiefly of alpha cells, and some hyper-

* These data are taken from the following sources: Campbell and Best (1938); Best, Campbell and Haist (1939); Marks and Young (1940); Bell, Best and Haist (1942); Wrenshall (1947); Wrenshall, Collins-Williams and Hartroft (1949).

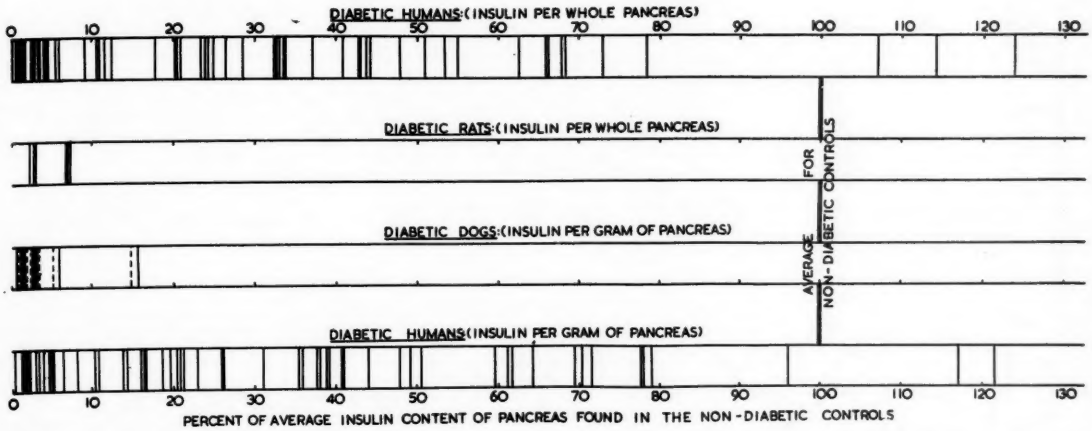

FIGURE 7 Extractable insulin of pancreas in experimental diabetes (dogs, wistar rats) compared with that found in human diabetics at autopsy. All results are expressed as percentages of the nondiabetic control value

plasia and vacuolation in duct epithelial cells. This description conforms with our own experience. The islets of Langerhans of all but one of the nine human subjects studied in this series, whose diabetes was diagnosed before the age of 20 years and was known to have been present more than one year before death, contained few recognizable beta cells.† On the other hand, as mentioned earlier, a majority of the adult diabetic subjects did not show pronounced loss of islet tissue. When the extractable insulin of pancreas for all of these human subjects is plotted against age at diagnosis of diabetes, it is found to increase abruptly after the second decade of life (Figure 6).

These findings suggest that diabetes mellitus in human subjects can be subdivided into *growth-onset* and *maturity-onset* types. In the former the diabetic condition becomes observable before full stature has been attained (approximately 23 years in the nondiabetic controls) and in the latter after this age (Figure 6).

For those subjects whose diabetes appears to have developed after the normal growth period, the extractable insulin of pancreas is very nearly independent of the duration of the diabetes (Figure 8).‡ Detailed

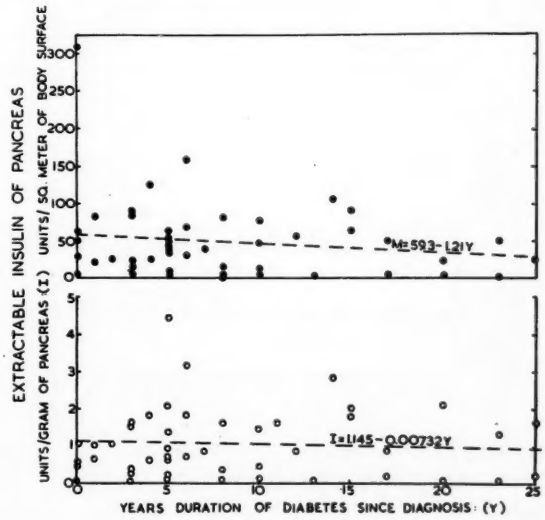

FIGURE 8 Linear regressions of units of extractable insulin per gram of pancreas and per square meter of body surface at autopsy on duration of diabetes after clinical diagnosis in subjects 27 years old or older at diagnosis of diabetes

† To supplement the few observations available on this topic, hematoxylin and eosin-stained sections of pancreas from 26 additional children dying in diabetic coma have been studied. In 22 of these there was marked reduction both in number of islets and number of cells per islet relative to nondiabetic subjects of comparable ages. There was no clear trend in the extent of these changes with the known duration of the diabetes.

‡ The equation of linear regression between concentration of extractable insulin (I) and years of diabetes duration since diagnosis (Y) for the maturity-type diabetics of this series is $I = 1.145 - 0.0073Y$. According to this trend, the diabetes would have to last for 124 years before the *concentration* of extractable insulin of pancreas would fall from one-half to one-tenth of the nondiabetic control value. On the other hand, it would have to last for only 39 years for a similar fall to occur if the extractable insulin of pancreas is expressed in terms of units per square meter of body surface. Either period of time is large compared with the average life expectancy of adult diabetic subjects.

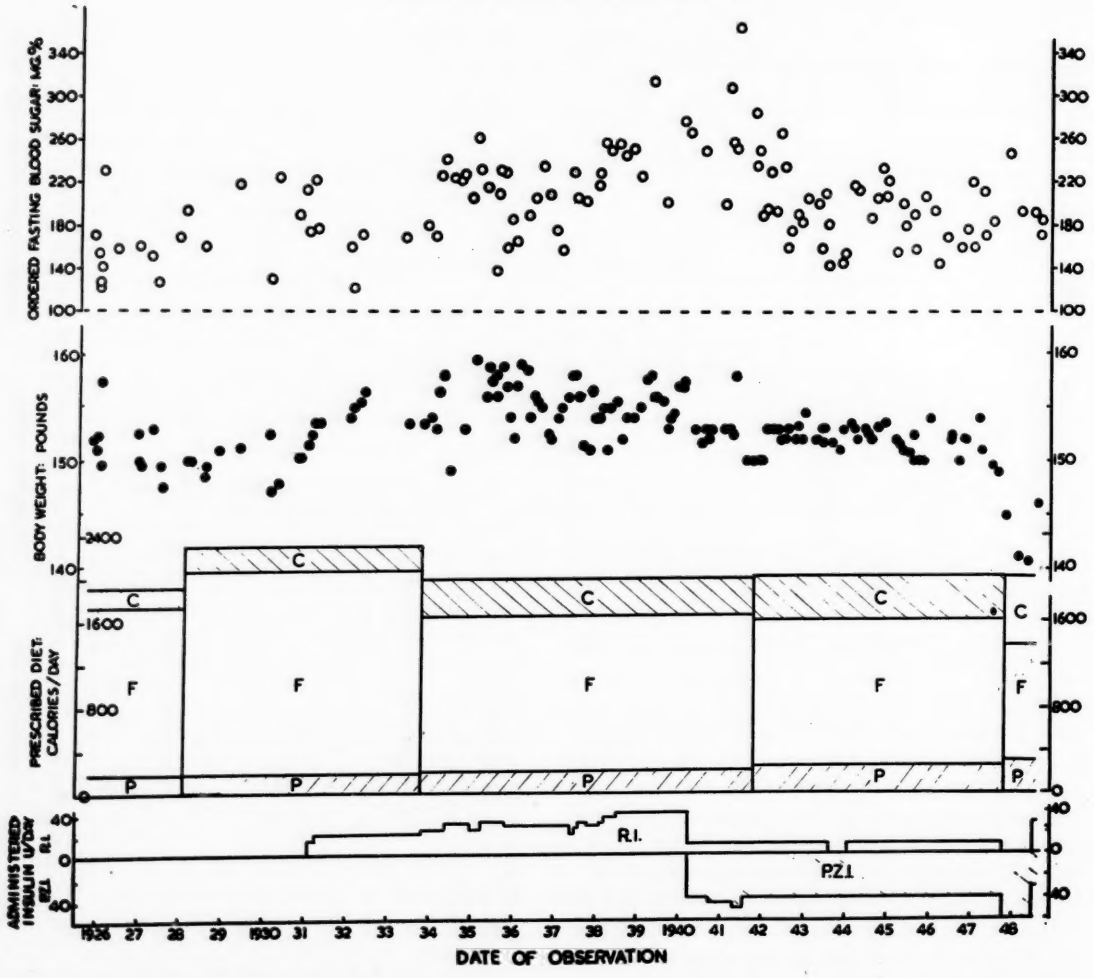

FIGURE 9 Clinical history of diabetes and therapy in a subject whose extractable insulin of pancreas falls within the limits for nondiabetics after a sequence of three different types of therapy. A262/48: female, 70 years old, 1.66 units of insulin/gram of pancreas, 108 units per total pancreas

study of the clinical histories of several of these subjects indicates that hyperglycemia was the rule rather than the exception through many years. An example of such a case is illustrated in Figure 9. A comparable history of diabetes in a maturity-onset diabetic subject whose extractable insulin of pancreas at autopsy was very low is shown in Figure 10.

The above differences between growth- and maturity-onset types of diabetes form a rational basis for explaining the great increase in life expectancy of diabetic children, as compared to that of diabetic adults, which accompanied and followed the advent of insulin therapy.

Either insulin therapy or the spontaneity of onset of diabetes in human subjects could represent factors responsible for the differences in the distribution of extractable insulin of pancreas observed in Figure 7 between these subjects and the experimental diabetes of animals. However, during the course of the present investigation, the extractable insulin of pancreas was measured in two male dogs which had developed spontaneous diabetes subsequently treated with protamine-zinc insulin during the remainder of their lives, and these animals provide some information on this subject. The diagnoses were made and insulin administered by the owners, both of whom were medical doctors. In spite of the type of onset of diabetes and insulin therapy, only trace amounts of insulin could be extracted from the

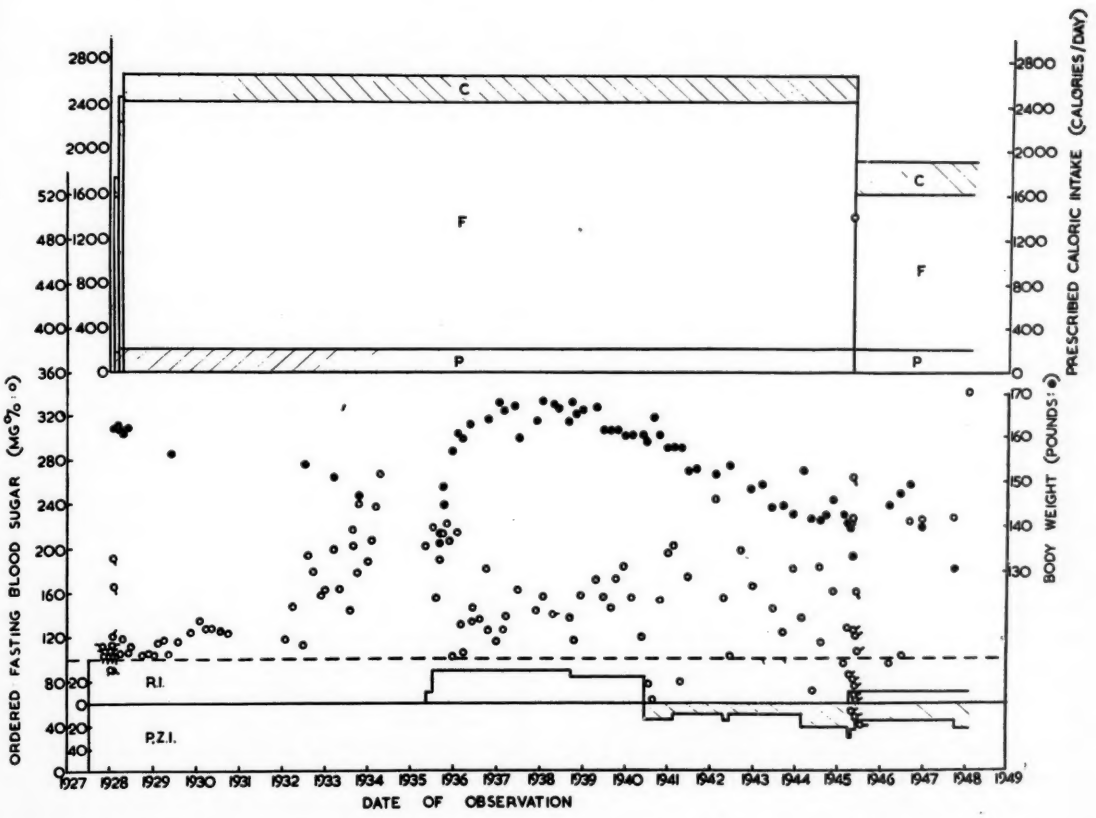

FIGURE 10 Clinical history of diabetes and therapy in a subject found to have a very low extractable insulin of pancreas at autopsy after a sequence of three different types of therapy. A28/48: male, 78 years old, 0.08 units of insulin/gram of pancreas, 2.5 units per total pancreas

pancreas at autopsy in one animal and at biopsy in the other. Histological data were obtained from only the biopsied dog and in this case the islets of Langerhans showed extreme atrophy, indistinguishable from that found in dogs with experimental diabetes of long standing, i.e., diabetes produced by anterior pituitary extracts, alloxan, or partial pancreatectomy.

12. *Effects of Diabetes Therapy on the Extractable Insulin of Pancreas in Human Subjects*

The extractable insulin of pancreas at autopsy in adult diabetic human subjects in relation to nondiabetic control subjects has been measured in three different eras of diabetes therapy. The relative values for these three eras are compared in Table 6. It is observed that the ratio of the insulin extractable from diabetic to nondiabetic pancreas is approximately the same in the three periods.

In the diabetic subjects of the present series treated with protamine-zinc insulin, there was no correlation between the extractable insulin of pancreas and the dose used (Table 7). However, the extractable insulin of pancreas decreases with increase in the proportion of subjects using insulin.

The absence of any marked effect of the duration of the diabetic state (Figure 8) or of prolonged hyperglycemia (Figure 9) on the extractable insulin of pancreas in mature diabetic human beings leads us to believe that factors other than these were more important in determining the histological condition of the islets of Langerhans and the extractable insulin of pancreas at autopsy in mature subjects. More data will be required to determine the nature of these factors.

13. *Extractable Insulin of Pancreas in Relation to Internal Factors Influencing the Release of Insulin*

Young has proposed (1939) and reaffirmed (Cotes,

TABLE 6 Ratio of the concentration of insulin extracted from the pancreases of adult diabetic subjects relative to nondiabetic controls: (a) shortly after the discovery of insulin (Pollak, 1926); (b) during a period of widespread use of regular insulin (Scott and Fisher, 1938); (c) during a period of widespread use of protamine-zinc insulin (present series, 1946-1951)

Source of Data	No. of Subjects		Av. Age of Diabetics (years)	Diab. Nondiab. Insulin Ratio	±S.E.
	Diabetic	Nondiabetic			
Pollak, 1926	9	5	53	0.34	±0.07
Scott and Fisher, 1938	14	15	59	0.30	±0.12
Present Series, 1946-1951	52	61	54	0.41	±0.08

Reid and Young, 1949) the hypothesis that growth hormone and the pituitary diabetogenic substance are identical. He assumes that the nitrogen retention required for a period of growth initiated by pituitary factors is, in turn, dependent upon the coexistence of an adequate supply of endogenous insulin. The development of diabetes as a result of the action of the pituitary factors is then interpreted as the result of an inadequate source of endogenous insulin. Since the formulation of this hypothesis, purified growth hormone preparations from the anterior pituitary gland have been shown to be diabetogenic in cats (Cotes, Reid and Young, 1949), and in dogs (Houssay and Anderson, 1949; Campbell, Davidson and Lei, 1950). Houssay (1947) has reported that the loss of islet tissue and decrease in the insulin secretion observed in animals treated with diabetogenic pituitary extracts are dependent on the combined action of the diabetogenic factor plus hyperglycemia.

If rate of increase in stature in the nondiabetic subjects of this series be taken as a measure of the normal activity of the growth hormone or hormones, then the large difference in the concentration of extractable insulin of pancreas which exists between growing and mature human subjects developing diabetes is understandable in terms of Young's hypothesis plus the experimental observations of the preceding paragraph. On this assumption, the differences in extractable insulin of pancreas and islet cell histology which characterize growth- and maturity-onset diabetes in human beings would represent the results of characteristic differences in the levels of growth factor in the tissues after the onset of diabetes. By this it is not inferred that the growth factor in question may represent more than a contributing factor in the etiology of growth-onset diabetes. It is inferred that the growth factor or factors normally present in children may produce important changes in the histology and extractable insulin of pancreas in the presence of diabetes.

The above interpretation may not be adequate in itself to account for all of the available data relating the extractable insulin of human pancreas and growth factors. In one adult subject of the series, onset of diabetes appears to have occurred more than 10 years after the appearance of acromegalic features. The diabetes was treated during the last year of life with diet and insulin (45 units P.Z.I. and 20 units R.I. per day) and at autopsy the extractable insulin of pancreas amounted to approximately 50 per cent of the average for nondiabetic adult controls. A majority of the fasting blood sugar values determined during the last month of life were above 200 mg. per cent.

Under the combined conditions of hyperglycemia and hyperactivity of pituitary growth factors, a much lower value for the extractable insulin of pancreas would be anticipated on the basis of the hypothesis outlined above. However, this would be expected only if a causal relationship existed between the pituitary

TABLE 7 Comparison of the extractable insulin of pancreas at autopsy with exogenous insulin dosage in adult human subjects whose diabetes was diagnosed one year or more before death and who used only protamine-zinc insulin (P.Z.I.) or no insulin therapy

Extractable Insulin of Pancreas		No. and Sex of Subjects	Av. Age in Years		Av. Per Cent Overweight at Death	Per Cent Using Insulin	P.Z.I. Dose/Day* Av.±S.E.
U/Sq. Meter Body Surface	Per cent of Av. for Control Group		At Diagnosis	At Death			
0-12	0-10	4F 5M	50	61	15	100	27.4±2.6
13-49	11-39	9F 6M	56	62	13	87	31.0±5.6
50-up	40-up	11F 5M	56	64	12	69	23.3±3.4

*Subjects of the group not using insulin are not included in this average.

hyperfunction and the diabetes in the patient, and only if the growth factors in the growth-onset type of diabetes and their effects are comparable to those in acromegalics with diabetes. Clarification of these possibilities must await the availability of further data.

There was no suggestion of overheight in the maturity-onset diabetics of this series, nor in such subjects referred to by Joslin, Root, White, Marble and Bailey (1946). In contrast to this, White (1932) found that 80 per cent of diabetic children were overheight at onset of diabetes. This difference serves both to resolve growth- and maturity-onset diabetics on grounds other than histology and extractable insulin of pancreas and to indicate the absence of abnormal activity of growth factors in the latter group during their youth. The absence of the gross abnormalities characteristic of acromegalics in the average maturity-onset diabetic, or of anterior pituitary-like substances, such as have been found in the urine of acromegalic subjects (Himsworth and Kerr, 1940), does not support the hypothesis that most cases of diabetes arising in mature subjects are caused by pituitary factors. Were such factors responsible for precipitating diabetes in mature subjects, it is surprising to us that the beta-cells and the extractable insulin of pancreas should not show progressive effects of its continuing diabetogenic action during the many succeeding years of diabetes or, in the absence of such a continuing action, that the signs of diabetes should not disappear.

Is the intermediate level of extractable insulin of pancreas found in most maturity-onset human diabetic patients an index of the rate of release of insulin into the blood stream? If so, is the rate reduced or brought to zero by pathological structures within the islets of Langerhans of such subjects? Histological evidence bearing on the latter possibility has been discussed by Gomori (1941) and by Hartroft (1950). If blockage of insulin release at the pancreas is adequate *in itself* to account for the symptoms of diabetes, it is to be anticipated that the rate of release of insulin from the diabetic pancreas would amount to approximately one-tenth or less of that observed in nondiabetic control subjects. If, on the other hand, no abnormal barrier exists to reduce the rate of release of extractable insulin from the pancreas, and if the extractable insulin of pancreas can be represented as a factor in a metabolic pool, then the average value for this factor in maturity-onset diabetics in relation to their nondiabetic controls is such that the rate of release should amount to approximately 50 per cent of the rate in nondiabetic controls. There is much speculation in these arguments.

Recent estimates have been made of the concentration of insulin in the blood of newly-diagnosed adult diabetic patients (Bornstein and Lawrence, 1951) and of nondiabetic adults (Bornstein, 1950) after taking a standard dose of glucose. The average concentration of insulin in the blood plasma of such adult diabetic patients was found to be approximately 80 per cent of the nondiabetic average under the conditions of observation. This suggests that, in these diabetic patients, release of insulin from the pancreas was not diminished. However, while it is interesting to speculate on the relationship between pancreatic and blood insulin levels, the available data are very few, and final judgment on the validity of the blockade hypothesis must await the accumulation of more data.

SUMMARY

The extractable insulin of pancreas has been measured at autopsy in 213 human subjects of whom 64 had diabetes mellitus, and in portions of pancreas removed at operation from 6 nondiabetic individuals. The measurements were expressed in terms of five different units and were correlated with clinical, pathological and laboratory data.

The hospitalized nondiabetic adult subjects of the series served as controls for the diabetic adult subjects with whom they were compared. The two groups corresponded closely in such factors as duration of terminal immobilization, assigned cause of death, hours postmortem of autopsy, body weight and height at autopsy and, to a lesser degree, in sex and age distribution.

The following conclusions were reached *for nondiabetic subjects:*

1. No appreciable change in the extractable insulin of pancreas occurred in hospitalized adult subjects with interval between death and autopsy or with days of confinement to bed preceding death. In hospitalized children there was no important trend in the concentration of extractable insulin of pancreas with hours postmortem of autopsy. It was found that units of extractable insulin per kilogram of body weight and per square meter of body surface were actually slightly higher in hospitalized than in sudden death subjects.

2. No significant sex difference in the extractable insulin of pancreas was found except for units per pancreas, which was lower for adult females than males in proportion to the average difference in body weight.

3. The concentration of the extractable insulin of human pancreas is lowest in the head and highest in the tail portion.

4. The concentrations of extractable insulin per gram of islet tissue and per gram of beta-cell tissue have been estimated with the help of other data to amount to approximately 1 per cent of the wet weight of the islet tissue, and to increase with age in human subjects.

5. Trends with regard to age indicate that an increase occurs in the extractable insulin of pancreas in passing from prematurity through birth, with a maximum reached at about six months after birth. This is followed by a shallow minimum which occurs in the third year of life. Thereafter the extractable insulin rises continuously, reaching the adult level between the twelfth and seventeenth years of life. Trends are less pronounced above this age, consisting generally of a slow decrease with advancing years, but with indications of a maximum in the fifth decade of life.

6. Evidence is presented indicating that biological variation rather than inaccuracies of measurement constitutes the principal source of the large standard deviations which exist in determinations of the extractable insulin of human pancreas.

7. In adult subjects, concentration of extractable insulin of pancreas was observed to increase progressively with decreasing weight of the pancreas. The subjects with the highest concentrations were characterized by obesity and fatty, yet small, pancreases. Variation of extractable insulin with size of the pancreas is no longer evident when the former is expressed as units per square meter of body surface.

8. Average values for the extractable insulin of pancreas differed little for patients grouped according to cause of death. Of these averages, only those for chronic and acute heart disease differed from the average for nondiabetic subjects after sudden death. The extractable insulin of pancreas showed increases of questionable significance in these two groups.

Several isolated conditions of special clinical or nutritional interest were included in the series. Both interstitial fibrosis of the pancreas and extensive hyalinization of the islets of Langerhans were found to be associated with low concentrations of extractable insulin of pancreas in nondiabetic adult subjects. The extractable insulin of pancreas in the four subjects at the extremes of overweight and underweight in the adult series were high and low, respectively. The concentrations of extractable insulin at operation were low in the removed portions of the pancreas in five out of six cases with unexplained hypoglycemia. They were also low in one adult and two children dying after extended periods of underalimentation, and in one child dying with glycogen-storage disease.

The following conclusions were reached *for diabetic subjects*:

1. The presence of diabetes mellitus was found to be associated with a lower average extractable insulin of pancreas than that in controls dying from the same assigned cause. The average extractable insulin of pancreas is found to increase continuously with age at death from very low values, in relation to controls, in young diabetic patients to a shallow maximum, amounting to half of the control levels, in diabetic patients dying in the fifth decade of life. In diabetic subjects whose diabetes was discovered during the normal period of growth (growth-onset type of diabetes mellitus) the extractable insulin of pancreas was very low in comparison to nondiabetic control subjects. It was much higher in a majority of subjects who had reached full stature prior to the discovery of the condition (maturity-onset type).

2. In the absence of demonstrable insulin resistance, the extractable insulin of pancreas at autopsy in 8 cases of diabetic coma was found to be extremely low.

3. In terms of islet-cell histology and extractable insulin of pancreas, only the growth-onset type of diabetes was found to be comparable with the meta-diabetes of dogs and rats induced by anterior pituitary factors, alloxan, or partial pancreatectomy.

4. Little demonstrable correlation with the extractable insulin of pancreas in the maturity-onset type of diabetic subject could be found for duration of diabetes, presence of prolonged hyperglycemia or type of therapy.

5. The possibility is considered that the characteristic atrophy of the islets of Langerhans and very low values for the extractable insulin of pancreas at autopsy in growth-onset type of diabetes may be related to the simultaneous presence of hyperglycemia and factors promoting active growth. The insulin-blockage hypothesis in the maturity-onset type of diabetes requires much further study before its validity is established.

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BIBLIOGRAPHY

Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Cambridge, Harvard University Press, 1913, pp. 480-492.

Anderson, E., and Long, J. A.: The effect of hyperglycemia on insulin secretion as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinology *40*:92-97 1947.

Bell, H. J., Best, C. H., and Haist, R. E.: The effect of partial pancreatectomy on the concentration of insulin in the pancreatic remnant. J. Physiol. *101*:11-16, 1942.

Best, C. H., Campbell, J., and Haist, R. E.: The effect of anterior pituitary extracts on the insulin content of pancreas. J. Physiol. 97:200-06, 1939.

——, Haist, R. E., and Ridout, J.: Diet and the insulin content of pancreas. J. Physiol. *97*:107-19, 1939.

Bliss, C. I.: The Design of Biological Assays. Ann. New York Acad. Sc. 52:877-88, March 10, 1950.

Bornstein, J.: Normal insulin concentration in man. Australian J. Exper. Biol. & M. Sc. *28*:93-97, 1950.

—— and Lawrence, R.: Two types of diabetes mellitus, with and without available plasma insulin. Brit. M. J. *1*:732, April 7, 1951.

Campbell, J., and Best, C. H.: Production of diabetes in dogs by anterior pituitary extracts. Lancet *234*:1444-45, June 25, 1938.

——, Davidson, I., and Lei, H.: The production of permanent diabetes by highly purified growth hormone. Endocrinology *46*:588-89, June 1950.

Cotes, P., Reid, E., and Young, F. G.: Diabetogenic action of pure anterior pituitary growth hormone. Nature, London *164*:209-11, August 6, 1949.

DuBois, E.: Basal Metabolism in Health and Disease, 3rd ed., Philadelphia, Lea and Febiger, 1936, pp. 120, 124.

Foglia, V. G.: Caracteristicas de la diabetes en la Rata. Rev. Soc. argent. de biol. *20*:21-37, April 1944.

Franklin, W., and Lowell, F. C.: On the preparation of human insulin for experimental use. J. Clin. Endocrinol. *9*:481-85, June 1949.

Gomori, G.: Observations with differential stains on human islets of Langerhans. Am. J. Path. *17*:395-406, 1941.

Haist, R. E.: Factors affecting the insulin content of the pancreas. Physiol. Rev. *24*:409-44, October 1944.

Hartroft, W. S.: The islets of Langerhans in man visualized by phase contrast microscopy. Proc. Am. Diabetes A. *10*:46-61, 1950.

Himsworth, H. P., and Kerr, R. B.: Pituitary-like factors in the blood and urine of diabetic patients and of animals treated with pituitary extracts. Clin. Sc. *4*:287-302, 1940.

Holt, L., and Fales, H.: The food requirements of children. I: Total caloric requirements. Am. J. Dis. Child. *21*:1-28, 1921.

Houssay, B. A.: The Role of the Hypophysis in Carbohydrate Metabolism and in Diabetes. Les Prix Nobel, 1947 (printed 1949), pp. 129-136.

—— and Anderson, E.: Accion diabetogena de hormonas hipofisarias purificadas. Rev. Soc. argent. de biol. *25*:91-112, July-August 1949.

Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, 8th ed., Philadelphia, Lea and Febiger, 1946, p. 68.

Marks, H., and Young, F. G.: Species variation in the insulin content of pancreas. Nature, London *146*:31-32, 1940.

Mirsky, I. A.: Some considerations of the etiology of diabetes mellitus in man. Proc. Am. Diabetes A. *5*:119-36, 1945.

Ogilvie, R.: A quantitative estimation of the pancreatic islet tissue. Quart. J. Med. *6*:287-300, 1937.

Pauls, F., and Bancroft, R.: Production of diabetes in the mouse by partial pancreatectomy. Am. J. Physiol. *160*:103-06, January 1950.

Pollak, L.: Ueber den Insulingehalt im Pankreas von Diabetikern. Arch. f. exper. Path. u. Pharmakol. *116*:15-34, 1926.

Scott, D. A., and Fisher, A. M.: The insulin and the zinc content of normal and diabetic pancreas. J. Clin. Investigation. *17*:725-28, November 1938.

——: Studies on the pancreas and liver of normal and zinc-fed cats. Am. J. Physiol. *121*:253-60, 1938.

White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea and Febiger, 1932, p. 198.

Wrenshall, G. A.: Alloxan Diabetes, M. A. Thesis, Toronto, 1947.

——, Collins-Williams, J., and Hartroft, W. S.: Incidence, control and regression of diabetic symptoms in the alloxan-treated rat. Am. J. Physiol. *156*:100-13, January 1949.

Young, F. G.: Anterior pituitary fractions and carbohydrate metabolism. I: The preparation and properties of diabetogenic extracts. J. Endocrinol. *1*:339-55, 1939.

DISCUSSION

DR. FRANCIS D. W. LUKENS *(University of Pennsylvania)*: This is the best presentation and the best source of information about the insulin content of the pancreas in diabetics with which I am acquainted. When one encounters a striking presentation of fact, one realizes that two things are going to happen: It is going to be quoted, as it should be, and it is going to be misquoted thoroughly, as it should not be. In this connection I should like to make one or two comments. In the first place, when anything is as carefully done as this work of Dr. Wrenshall and his colleagues, it is easy to accept the results without criticism. For the most part this is proper, but we should realize that the investigators have had to make certain arbitrary definitions, and I would like to mention one. Dr. Wrenshall referred, I think, to the fact that if a tenth of the pancreas is

left surgically, an experimental animal may not have diabetes. I am sure that that has been true. I am also sure that animals have developed diabetes spontaneously after a quarter or even as much as half of the pancreas has been left in place. In other words, here is a useful point, but one that may have to be interpreted somewhat.

I should also like to ask one question. Have the authors measured the insulin content of the pancreas of *normal* subjects who, for this purpose, have been given insulin for a day or two before death? In view of the work from their laboratory on the fact that insulin administration to animals lowers the insulin content of the pancreas and in view of the fact that the diabetics presumably receive insulin, this kind of control experiment might be suggested.

Far more important than these technicalities, which I merely suggest in passing, is the fact that when one sees a striking result of this kind in which a group of young diabetics have practically no insulin and in which a group of elderly diabetics contain, shall we say, 50 per cent of the normal amount of insulin, one must have some frame of reference in which to place the results if they are to be quoted and used correctly.

I should like to suggest one or two of the points of reference that we must have in mind. The content of insulin must first of all be related to its rate of secretion. Dr. Wrenshall has recognized this difficulty. As far as I know, there is a fairly good correlation between concentration and capacity to secrete insulin, if one compares the results obtained in Dr. Best's laboratory and in Professor Houssay's laboratory. However, this relationship between content and secretion must still be accepted with caution.

Insulin content must also be related to the fate of the insulin formed and secreted. It appears that one of the functions of insulin is to combine with tissue and to exert its effect upon the tissues, and it is quite clear that there are three conditions which interfere with this, which I will list. First of all, there are the metabolic needs or stresses, of which Dr. Long's diagram on the increased insulin needed to maintain fat deposits is a thought-provoking example. If any situation such as this occurs, 50 per cent of insulin may become far less than the actual need of the obese patient. Secondly, we have contra-insulin hormones, and thirdly, we have antibodies against insulin which we see in the rare patients with allergy to insulin. These have been recently studied by Stadie in connection with the combination of insulin with the rat diaphragm in vitro. He has found it possible to measure an interference with this action of insulin, by pre-treating the rats with suitable hormones. A similar interference with the union of insulin and diaphragm is produced by antibodies to insulin in the serum of insulin-resistant patients. This means that regardless of how much insulin is formed or secreted by the pancreas, the availability of that insulin to the tissues becomes the ultimate consideration with which we have to deal.

I make these comments simply in order that we can see that the very brilliant facts so clearly presented here are part of a complex picture; they will be valuable to us because they fill in one more gap in that picture.

DR. FREDERICK M. ALLEN *(New York):* Years ago we published microphotographs showing that children who could not be made or kept sugar free by starvation had practically complete absence of islands in the pancreas. On the other hand, in the older and milder cases which could thus be kept free, there was corresponding evidence of islands in the pancreas. I would suggest this test of how easily individuals can be starved sugar free or kept sugar free on certain diets .If they can be kept sugar free, the insulin is there. Also, as another problem regarding the patients in whom islands are reported more or less abundant, I think close study will show that those islands are frequently peculiar in not only number but configuration and perhaps cells, giving some evidence that "a storm has passed over the islands," as Heiberg once expressed it.

This can be illustrated experimentally by my published observation that by temporarily ligating the pancreas and thus setting up a secondary inflammation, it is possible to destroy the islands more or less completely, leaving the glandular tissue unchanged and free from fibrosis. This may be of importance for the etiology of quite a few cases, especially of youthful diabetes, in which an infectious pancreatitis may be transitory and undiagnosed but may leave permanent diabetes.

This dovetails with the paper yesterday on hyperinsulinism, because it is possible thus to destroy island tissue. If surgeons would take care to avoid the danger of fat necrosis, they could destroy the abnormal islands without resecting the pancreas. This fits into my other work on cancer for the past eighteen years. From rat experiments I passed on to publishing human cases showing that by setting up this type of reaction by ligation for a suitable number of hours, it is possible selectively to destroy either sarcoma or carcinoma. Therefore, the malignant island cells might all the more easily be destroyed by this method even if they have invaded structures which cannot be excised. I think

this is theoretically important as a specific reaction which can selectively destroy one type of tissue as against another. In practice I hope it may prove useful for some tumors of the extremities, head, neck, tongue, larynx, etc., and I invite trials.

DR. GERALD A. WRENSHALL (Closing): Dr. Lukens has been very generous in his appraisal of our paper. He asked concerning the effect of administered insulin on the extractable insulin of pancreas in nondiabetic subjects. We had one subject in our series with acute pancreatitis who received 20 units a day of regular insulin for 43 days before death. The value which we found for the extractable insulin of pancreas was about 60 per cent of the nondiabetic average.

Dr. Allen brought up an important point not dealt with in the presentation. If an adult-onset type diabetic is overweight, our results make it appear reasonable to conclude that reduction of overweight, or removal of any such reversible factor which is causing the diabetes, might restore the subject's ability to control his diabetes without exogenous insulin in a majority of cases.

Our results, I think, also indicate the essentiality of insulin in the therapy of growth-onset type diabetes.

OBSERVATIONS ON THE DUTIES OF A PHYSICAN

Let me advise you, in your visits to the sick, never *to appear in a hurry, nor to talk of indifferent matters, before you have made the necessary inquiries into the symptoms of your patient's disease.*

Avoid making light of any case. "Respice finem" should be the motto of every indisposition. There is scarcely a disease so trifling, that has not, directly or indirectly, proved an outlet to human life. This consideration should make you anxious and punctual in your attendance upon every acute disease, and keep you from risking your reputation by an improper or hasty prognosis.

Do not condemn, or oppose, unnecessarily, the simple prescriptions of your patients. Yield to them in matters of little consequence, but maintain an inflexible authority over them in matters that are essential to life.

Preserve, upon all occasions, a composed or cheerful countenance in the room of your patients, and inspire as much hope of a recovery as you can, consistent with truth, especially in acute diseases. The extent of the influence of the will over the human body has not yet been fully ascertained.

Make it a rule never to be angry at anything a sick man says or does to you. Sickness often adds to the natural irritability of the temper. We are, therefore, to bear the reproaches of our patients with meekness and silence. It is folly to resent injuries at any time, but it is cowardice to resent an injury from a sick man, since, from his weakness and dependence upon us, he is unable to contend with us upon equal terms. You will find it difficult to attach your patients to you by the obligations of friendship or gratitude. You will sometimes have the mortification of being deserted by those patients, who owe most to your skill and humanity. This led Dr. Turner to advise physicians never to choose their friends from among their patients. But this advice can never be followed by a heart that has been taught to love true excellency, wherever it finds it. I would rather advise you to give the benevolent feelings of your hearts full scope and to forget the unkind returns they will often meet with, by giving to human nature—a tear.

—From a lecture given by Benjamin Rush, M.D., to the University of Pennsylvania, Philadelphia, February 7, 1789. Reprinted in the *American Journal of Medicine*, November 1951.

The Role of the Ketone Bodies in the Etiology of Diabetic Coma

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There is still no agreement as to the specific cause of the coma that results from uncontrolled diabetes mellitus. Differences of opinion are the natural result of conflicting experimental data on the subject.

Is acidosis itself the cause of coma? There seems to be no convincing evidence that it is, and there is much good evidence showing that it is not. Practically all recent writers share this opinion, although as recently as 1946 Peters and Van Slyke considered the acidosis itself a very important factor.

Are the ketone bodies the cause of diabetic coma? Many authorities hold this opinion. For instance Joslin, in his most recent text, states that "the clinical picture of diabetic coma (is) . . . attributable in a large part to the toxic effects of the ketone bodies." Others, including MacKay, Bertram, Baker and Brugel have denied that this is true. Evidence can be found to support both views. Recent writers, including Kety, Barach, Root, Soskin, and Best and Taylor, have given cautious, nonspecific conclusions.

There seems to be no valid evidence to refute the statements of Root and Brugel that diabetic acidosis does not exist without ketosis. Exhaustive search of the literature has failed to disclose even one case of unquestionable diabetic acidosis in which blood ketone concentration was shown to be normal.

In 1938, Schneider and Droller concluded from their own experimental work in giving sodium acetoacetate to rabbits by intravenous infusion that "diabetic coma is due in the main to a specific intoxication by the acetoacetic anion." This conclusion seems surprising in view of the disagreement that existed up to that time. An attempt was therefore made to repeat their experiments.

EXPERIMENTAL OBSERVATIONS

Schneider and Droller performed their experiments on rabbits using constant intravenous infusions and obtained blood samples for quantitative ketone analysis at the onset of signs of severe abnormality in the animal. Using the sodium salt of acetoacetic acid in isotonic concentration, they gave up to 400 cc. in one hour to each of four rabbits. No abnormalities were noted so that blood ketone analyses were not performed. They believed they were not giving "sufficient" sodium acetoacetate so they used a solution 0.4 normal—which is about 2½ times hypertonic with blood—and they produced coma readily in each of five rabbits, using quantities up to 175 cc. over similar time intervals. When one reduces their figures to grams of acetoacetate given, it is found that they gave

From the Diabetic Coma Project, Metabolic Laboratories, Philadelphia General Hospital. Presented at the Annual Meeting of the American Diabetes Association, Atlantic City, N. J., June 1951. Based on data published in *The American Journal of The Medical Sciences*, April 1951.

as high as 5.9 grams in a one-hour period in isotonic concentration without producing apparent abnormalities, yet four rabbits given less than 5.9 grams went into coma when it was given in a hypertonic solution. There is strong reason to suspect, therefore, that the results obtained may be artefacts of the concentrations used rather than the total dosage per unit of time of the specific agent used.

Our experiment was as follows: Infusions were made into an ear vein of rabbits at a constant rate by the Schneider and Droller technic. Table 1 shows representative data. It can be seen that the volume of the solution injected was apparently not an important factor. In a control experiment one rabbit tolerated 540 cc. of isotonic saline over a period of 175 minutes without abnormal signs becoming apparent. This amount was probably over three times the blood volume of that rabbit. Large amounts of acetone were toxic, but the blood acetone concentration had to be very much higher than that found in diabetic acidosis to produce abnormalities. Rabbits given isotonic solutions of sodium acetoacetate showed no abnormalities even though high blood levels were reached. Four rabbits were given hypertonic saline solution at about the same hypertonicity of the sodium acetoacetate used by Schneider and Droller and using the same quantity of fluid at a similar rate. Each of these rabbits died or went into coma.

We reach the following conclusions from these experimental observations:

1. Hyperketonemia can be produced in rabbits in the range found in human diabetic acidosis and maintained for several hours without apparent toxic effects upon the animal.

2. Hypertonic saline solution of about three times the tonicity of plasma can cause death in rabbits when injected intravenously. Death is apparently the result of the hypertonicity itself and not the volume of fluid injected, the rate of the infusion, or the amount of sodium chloride given.

3. The toxicity noted in the experiments performed by Schneider and Droller was apparently the result of or greatly influenced by the hypertonicity of the solution injected and not necessarily the result of the specific agent or quantity of agent infused. This casts definite doubt on the validity of their conclusions.

CLINICAL OBSERVATIONS

The data obtained on 42 patients in severe diabetic acidosis who were studied at the Philadelphia General Hospital showed only limited correlation between the blood ketone concentration and the mental state before and during therapy (Tables 2 and 3). There was great individual variation. One patient with a normal mental state had a blood ketone concentration higher than the average of the group that was totally unresponsive and higher than any patient who was

TABLE 1 THE EFFECTS OF INTRAVENOUS INFUSIONS IN RABBITS

Solution Infused		Quantity Infused (ml.)	Duration of Infusion (min.)	Blood Total Ketone Concentration as Acetone* (mg. %)	Results
Saline	0.85%	540	175		Normal
Saline	2.10%	280	85		Coma at 78 min.
Acetone	1.74%†	120	44	175.9 at 50 min.	Coma at 44 min., full recovery
Sodium Aceto-Acetate	1.51%‡	150	85	63.0 at 85 min.	Normal

*Total ketone concentrations listed above are comprised almost entirely of the single agent infused. These quantities represent concentrations of the agent in excess of those generally found in human diabetic acidosis
† The value for this item in molarity is 0.3M.
‡ The value for this item in normality is 0.14N.

TABLE 2 THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION BEFORE THERAPY

Mental State*	Number of Patients in Group	Mean Blood Total Ketone Concentration, Expressed as Acetone (mg. %)	Standard Deviation	Range	
				High	Low
1	11	60.1	26.9	123.0	34.9
2	13	73.4	24.4	111.8	25.8
3	7	85.0	35.6	117.0	21.0
4	11	109.8	37.4	154.0	47.7

*The mental state is described as follows: 1. normal; 2. lethargic; 3. unconscious, responds to painful stimuli, reflexes intact; 4. unconscious, no response to painful stimuli, reflexes absent

TABLE 3 THE RELATIONSHIP BETWEEN MENTAL STATE AND BLOOD KETONE CONCENTRATION DURING THERAPY

Patient	Interval after Onset of Therapy (hrs.)	Mental State	Blood Total Ketone Concentration, Expressed as Acetone (mg. %)
M. P.	0	1	123.0
	12	2	46.4
A. R.	0	2	80.0
	3¼	2	59.6
	8½	2	25.2
	18	2	2.8
A. M.	0	3	53.3
	3	2	72.0
	9	2	59.0
	22	2	19.0
	27	3	18.1

*Mental state is described as follows: 1. normal; 2. lethargic; 3. unconscious, responds to painful stimuli, reflexes intact

in coma with reflexes still intact. One unconscious patient had a blood ketone concentration lower than the average of the group that was normal mentally.

Follow-up data were obtained during therapy of 14 patients in an attempt to relate the changes of mental state to the blood ketone concentration after treatment was started. In 11 patients, the trend of the blood ketone concentration was toward normal as were all the metabolic abnormalities in the patients who recovered. The blood ketone change did not correlate well with the mental state in many cases. The condition of one patient appeared to be improving clinically when the blood ketone concentration rose, and then deteriorated when the blood ketone concentration decreased. Shortly before death the patient again lapsed into coma though the ketone concentration was at its lowest recorded level.

SUMMARY

There is essential agreement that all ketone bodies can cause toxic effects if given in large dosages. The question as to whether they are toxic in the concentrations found in the blood of patients in diabetic acidosis is still not definitely answered. Duration of exposure to ketosis may be as important a factor as the degree of hyperketonemia. A similar situation in regard to ether administration is well known. The fact that ketosis is an absolutely constant finding in diabetic acidosis points naturally to a strong relationship between them. But even though individual response to drugs varies greatly, if the ketone bodies themselves are the dominant factor in the production of diabetic coma, then some reasonable correlation should exist between the blood ketone concentration and the mental state. All observers agree that there is a correlation on the average, but with tremendous overlap; and in all of the reports on animal experimentation, there is poor correlation of the blood ketone concentration to the appearance of the animal. Even if there were good evidence of ketone toxicity, and even if there were good correlation of the mental state and blood ketone concentrations, the fact that a substance *can* be toxic does not necessarily mean that it *is* the cause of a particular clinical syndrome.

CONCLUSIONS

1. Acidosis per se does not seem to be the main cause of diabetic coma, though it probably plays an important role in the production of some symptoms.

2. It is very unlikely that the ketone bodies are the primary cause of diabetic coma. It seems more reasonable to view their presence as an indicator of the metabolic derangements without particular toxicity in themselves, just as the blood urea is a non-toxic indicator of uremia.

3. It has been shown frequently that many factors must contribute to the clinical appearance and prognosis of the patient in diabetic acidosis. These probably include the severity of the diabetes, the age and general health of the patient, the degree and duration of acidosis and ketosis, the serum potassium concentration, the existing complications, and so on.

4. It is possible that there is a potent factor as yet unknown that may be the dominant feature of diabetic coma.

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REFERENCES

[1] Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, Williams and Wilkins, 1946, vol. 1, p. 511.

[2] Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: Treatment of Diabetes Mellitus. 8th ed. Philadelphia, Lea & Febiger, 1947, p. 427.

[3] MacKay, E. M.: The significance of ketosis. J. Clin. Endocrinol. *3:*101-10, Feb. 1943.

[4] Bertram, F.: Pathogenese und prognose des coma diabeticum, Ergebn. d. inn. Med. *43:*258-365, 1932.

[5] Baker, T. W.: A clinical survey of one hundred and eight consecutive cases of diabetic coma. Arch. Int. Med. *58:*373-406, Sept. 1936.

[6] Brügel, H. G.: Über das verhalten des ketonkörperspiegels in coma diabeticum. Klin. Wchnschr. *20:*89-94, 1941.

[7] Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F.: Blood flow and oxygen consumption of human brain in diabetic acidosis and coma. J. Clin. Invest. *27:*500-10, July 1948.

[8] Barach, J. H.: Ketosis in health and disease. Am. J. Digest. Dis. *10:*134-38, Apr. 1943.

[9] Root, H. F.: The use of insulin and the abuse of glucose. J. A. M. A. *127:*557-64, March 1945.

[10] Soskin, S., and Levine, R.: Physiological and clinical aspects of ketosis. Am. J. Digest. Dis. *2:*305-13, Oct. 1944.

[11] Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice. 4th ed., Baltimore, Williams and Wilkins, 1945, p. 574.

[12] Schneider, R., and Droller, H.: The relative importance of ketosis and acidosis in the production of diabetic coma. Quart. J. Exper. Physiol. *28:*323-33, 1938.

DISCUSSION

DR. EDWARD S. DILLON *(Philadelphia, Pa.):* We have been interested for many years in the reasons why diabetic patients, receiving inadequate treatment, go into coma and die. We clinicians are well aware that many complex chemical and physiological abnormalities appear, but in our thinking we are likely to consider these abnormalities the result of acidosis and particularly ketone acidosis.

Is death due directly to the acidosis per se? Years ago, in studying 268 coma cases, we found that the prognosis was not closely related to the degree of acidosis as measured by the carbon dioxide combining power. Furthermore, if the acidosis itself is the killing factor, why is it that alkali therapy does not play a larger and more effective role in the treatment?

Many of us are apt to feel that the acidosis is particularly noxious because it is a ketone acidosis, and that the hyperketonemia is the cause of death. The experimental data in the literature are confusing; the fact, which Dr. Fisher points out, that ketone bodies cause death only when given in hypertonic solution has not previously been pointed out, so far as I know.

Please note that in the clinical studies on 42 patients there was little correlation of the outcome with the degree of hyperketonemia.

The best correlation in any studies at our hospital was in connection with the oxygen uptake in the brain; this work done by Kety was reported at this meeting three years ago. He found that the normal oxygen consumption in the brain was 3.5 cc. per 100 gm. of brain per minute, and whenever it fell to 2.1 cc. unconsciousness invariably resulted. What does this low consumption of oxygen represent? Is it a matter of phosphorylation going on within the brain? Perhaps that is the answer. I do not know.

DR. SAMUEL SOSKIN *(Chicago, Ill.):* I think most workers will agree that there is nothing peculiarly toxic about the ketone bodies. They are just about as toxic as any other acid that produces a similar acid-base disturbance. We should not forget the work of Woodyatt and his group in the early twenties; they attempted to produce a disturbance of acid-base balance in animals with hydrochloric acid, and by and large got about the same clinical results.

On the other hand, we should clearly understand what is meant by the statement that the ketone bodies are not a specific and direct cause of diabetic coma. The fact is that there is no single cause of coma. It is the end result of a combination of circumstances or chain of events, but certainly the initiating incident is the over-production of the organic acids. Once that begins, it is not long before the loss of fluid and salt begins to introduce a shock-like state into the picture, not very much different from surgical shock. After all, people do die from surgical or traumatic shock, even when diabetes and ketone bodies are not involved.

I believe that a third factor, which enters the picture a little later, is liver failure. Diabetic dogs from which insulin is withheld develop their maximum ketosis on about the third or fourth day. From that point on to about the seventh or eighth day, when they usually die in coma, the ketone bodies fall. That is, as the animal deteriorates, he has less and less ketone bodies in the blood and urine. The same is true of other types of experimental diabetes as well as that following pancreatectomy. Biopsy of the liver of such an animal at the time when the ketones are falling but the clinical state of the animal is getting worse, or postmortem examination, reveals that the liver is a mass of fat; it is hard to distinguish any normal architecture. Indeed, if you produced that degree of liver damage by any other means, you would expect the animal to die.

So I may summarize by saying that there is a chain of events in which the final result cannot be ascribed merely to the presence of ketone bodies. Therefore, you cannot expect to find any correlation between the level of ketone bodies and the state of the patient. There is first, acidosis; second, shock; and finally, liver failure.

The Discovery of Pancreatic Diabetes

THE ROLE OF OSCAR MINKOWSKI

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In 1889 von Mering and Minkowski reported that total pancreatectomy in dogs was followed by severe diabetes. This was a discovery of historic importance. It demonstrated that diabetes occurs in the absence of the pancreas; and this finding furnished the starting point for research which proved that this organ produces an internal secretion, thus leading to the discovery of insulin and its application to the treatment of patients suffering from diabetes. Studies on carbohydrate metabolism were considerably extended, and it became possible to demonstrate the role of the liver in this metabolism and the regulatory functions of hormones secreted by several endocrine glands in normal conditions and in diabetes. This work was done in the laboratory of the Medical Clinic at the University of Strassburg, under the direction of Professor B. Naunyn, who in his book "Erinnerungen, Gedanken und Meinungen" refers to it in a statement which can be translated as follows:

"The discovery of pancreatic diabetes by von Mering and Minkowski gave a powerful impetus to our experimental research in diabetes. They had had a conversation about the extirpation of the pancreas. Next day Minkowski recounted that von Mering had upheld the dogma, accepted since Claude Bernard, that animals did not survive total pancreatectomy. He, Minkowski, had maintained that in dogs survival was possible; what did I think about it? I said: 'Since you have been able to remove the liver, you will also be able to carry out the removal of the pancreas, and if geese survive the liver operation, dogs will come through this one with even greater ease.' The next day Minkowski performed the first pancreatectomy in my laboratory; Mering assisted and then left on a trip. When Minkowski returned to the laboratory, 24 hours later, he could already report that the dog had severe diabetes with 5 per cent sugar. Incidentally, as long as he was in Strassburg, Mering did not perform pancreatectomy on his own, nor did he attempt to, and took little interest in following up the discovery."

When Naunyn's book was published, Thierfelder, a pupil of von Mering, wrote the following letter to Minkowski on May 5, 1926:

"You will be surprised to receive a letter from me. In fact, a special circumstance makes me write to you. It has to do with the description of the discovery of pancreatic diabetes given by Naunyn on page 457 of his 'Erinnerungen' (Memoirs). That description is undoubtedly mistaken, or at least incomplete. It not only minimizes Mering's contribution to this discovery, it completely suppresses it. This cannot remain unanswered, because it is already becoming current in medical literature. Thus, in the book written to commemorate the sixtieth birthday of Ludolf Brauer (reprint

from the *Zentralblatt für Herz-und Gefässkrankheiten,* 1925, p.2), Büdingen says: 'According to Naunyn, his great teacher, this discovery of genius should be attributed solely to Minkowski; von Mering only helped him in the operation.' Because of my friendship with von Mering while he lived, you will understand that it appears to me to be my duty to defend his interests also after his death. Would you not wish to make use of the occasion to correct Naunyn's version in some appropriate place?"

I asked Minkowski's wife, who is now living in Buenos Aires, for information about the discovery of pancreatic diabetes and she gave me a copy of the letter written by Minkowski in answer to Thierfelder. This letter, written from Breslau and dated May 8, 1926, says:

"You are not fair to Naunyn if you imagine that in his account of the discovery of pancreatic diabetes he has unjustly belittled von Mering's contribution. Naunyn, as director of the Institute where the work was carried out, and as editor of the *Archiv für experimentelle Pathologia und Pharmakologie* in which it was published, kept in touch with the development of this research and guided the authors of the manuscript. Thus all that he wrote in his memoirs in his desire to be 'truthful even to harshness,' was very familiar to him.

"Nothing is further from my mind than the wish to detract from von Mering's memory. I never quarreled with him; I was friendly with him until his death and I always felt grateful to him for having suggested the operation of pancreatectomy to me in a conversation we had. I do not think he had any grounds for complaint of my behavior, at any rate he never expressed any, either on his visit to me in Cologne shortly before his death or when I returned his visit in Halle. There were, however, good reasons (and he agreed with them) why all the communications on pancreatic diabetes, such as those to the Medical and Natural Science Society of Strassburg, the First International Congress of Physiology at Basel, the Assembly of Natural Science Research Workers at Heidelberg and the Congress of Internal Medicine at Leipzig, should be presented by myself alone, and also why our joint work in the *Archiv für experimentelle Pathologie und Pharmakologie* should have been written by me only. The same reasons explain why further work on diabetes should be conducted by me while von Mering, as far as I know, did no further experimental work on the problem.

"I am sorry I did not publish a detailed history of the discovery of pancreatic diabetes while von Mering was still alive, as he could only have confirmed my statements. It is not very pleasant for me to do so after his death because my account of the affair can easily be misinterpreted. Personalities seem to me to be of no importance compared with the value of positive results. However, your prejudice against Naunyn's statements forces me to describe exactly what happened as it has remained engraved in my memory.

"You know I worked in the laboratory of the Medical Clinic at Strassburg while von Mering was working at Hoppe-Seyler's Institute when you were an assistant there. One day in April 1889 I went over to your Institute to consult some chemical periodicals in your library, which were not available in our Clinic, and there I met von Mering, who shortly before had recommended 'Lipanin,' an oil with 6 per cent free fatty acids, as a substitute for cod liver oil in the belief that its favorable therapeutic effects might be due to its free fatty acid content.

" 'Do you use Lipanin frequently in your clinic?' von Mering asked me.

" 'Oh, no,' I answered. 'We give our patients only good fresh butter, not rancid oil.'

" 'Don't scoff,' he replied. 'Healthy men must split fats before absorbing them. If, however, the pancreas does not function properly, fats already split must be given.'

" 'Have you proved this experimentally?' I asked.

" 'That is not so easy,' he answered, 'since pancreatic lipolytic enzymes pass into the gut even if one ties the pancreatic duct.'

" 'Well, then,' I said, 'remove the whole pancreas!'

" 'That is an impossible operation,' he replied.

"As I did not know that Claude Bernard had stated that animals could not be kept alive after total pancreatectomy, and my youth led me to presumptuous overestimation of the results I had already obtained in my surgical experiments, I exclaimed: 'Bah! there are no impossible operations; pancreatectomy cannot be more difficult than hepatectomy; give me a dog and I will remove its pancreas today.'

" 'Good, I have dog which I can let you have now. So try it.'

"That same afternoon in Naunyn's laboratory, with von Mering's help, I took out his dog's pancreas. Perhaps, as a lucky coincidence, that particular animal possessed especially favorable anatomical conditions; they vary considerably in different animals. The whole gland was removed and the abdominal wall sutured; the animal remained alive and apparently well for nearly four weeks. I intended to return it to von Mering for his experiments on the utilization of fats, so I did not bother much about it; but because there was no suitable cage available it was kept tied up in one part of the laboratory. The day after the operation, von Mering had to go to Colmar urgently because his father-in-law was seriously ill with pneumonia. He had to stay there over a week. Meanwhile the dog, which was house-trained, very often micturated in the laboratory. I scolded the servant for not letting it out frequently enough, but he said: 'I do, but the animal is queer; as soon as it comes back it passes water again even if it has just done so outside.'

"This observation induced me to collect some of the urine in a pipette and do a Trommer's test. Finding the urine reduced strongly, I made a 10 per cent solution

with 1.5 cc. I still had in the pipette and found it contained 12 per cent sugar.

"I thought at first that the glycosuria might be due to the fact that von Mering had treated his dog for a long time with phloridzin. So I immediately pancreatectomized three more dogs with no sugar in their urine previous to the operation. The second and third animals died two days later of necrosis of the duodenum, but both had glycosuria before they died. The fourth animal survived and from the second day after pancreatectomy had a persistent diabetes just like the first animal's.

"It was then von Mering returned, but did not come at once to the laboratory. I met him again on the first of May, the Anniversary of the foundation of Strassburg University at the festival celebration in the auditorium. Purely by chance, I was sitting behind him and I said over his shoulder, 'Do you know, von Mering, that all pancreatectomized dogs become diabetic?'

" 'That's interesting,' he replied, 'we must follow up this question.'

"I then operated on a whole series of dogs, assisted sometimes, but not always, by von Mering. Once he tried to operate, but the animal died of hemorrhage on the operating table so he gave up trying.

"He took part in some of the work, in particular the glycogen determinations with which he was familiar. He was prevented by other circumstances from coming regularly to the laboratory of the medical clinic and he left me to finish the work alone. At the end of the semester I proposed to von Mering we should publish the results of our research together and that I would carry on the further conduct of the work alone. He agreed and also left me to prepare the manuscript of our work. When it was finished and ready for the press, von Mering was away on vacation and as I did not wish to delay its publication, I was unable to let him see it. Naunyn had no scruples about publishing the manuscript I had prepared in his *Archives,* so von Mering read the paper for the first time in proof and praised its make-up. Because I had written it, I put his name first, out of courtesy and also because von Mering was somewhat older than I and his name came before mine in alphabetical order. It is curious that because of that order, 'von Mering and Minkowski,' some have inferred that von Mering's contribution was necessarily greater than mine.

"Naunyn, who was in a position to judge, considered I had shared too much with von Mering in not keeping the work on diabetes for myself and leaving him to follow up the further work on fat absorption. I knew, however, that I owed the discovery of diabetes to a lucky accident, and that I had not, any more than von Mering, imagined until then the importance the pancreas had in carbohydrate metabolism. Moreover, perhaps I would never have tried the extirpation of the pancreas if that conversation with von Mering had not taken place. I thought it only decent to invite him to collaborate in the work on diabetes, and I have never omitted to place his name together with mine even in recent times, as for example in my report on insulin in the Kissingen Congress of 1924.

"You must remember that in work done over many years I alone defended the doctrine of pancreatic diabetes and the internal secretion of the pancreas against many attacks, in particular against those of Edward Pflüger; also that I have contributed new proof of my ideas by experiments with transplants, duodenal extirpation, etc. In all these discussions von Mering took no part or interest. It is also peculiar, perhaps because he did not master the technique of pancreatectomy, or because he had no further interest in the problem, that he did not resume the work on fat absorption after pancreatectomy. With his consent, I suggested that Mr. Abelman in the laboratory of Naunyn's clinic should examine fat absorption after pancreatectomy. Later Burkhardt and Lombroso in my clinic in Greifswald busied themselves with this question which even today merits further research.

"I do not intend to publish this information. I shall, however, leave a copy of this letter in a suitable place, for at some future time a student of the history of diabetes may be interested in the true facts. Only if you or anybody else were to take a definite attitude against Naunyn's account, would I consider myself obliged to take action to clarify the circumstances."

It is not worth while to report or discuss the innumerable versions of the story of the discovery of pancreatic diabetes, some of which have been published while others have passed into the oral tradition of laboratories.

Professor E. Frank, now of Istanbul, and himself a pupil of Minkowski, is in possession of a copy of this letter and quotes its contents in his book written in 1949. The letter was deposited by Minkowski in the Medical Section of the "Schlesiche Gesellschaft für Vaterländische Kultur" in Breslau. When Hitler came to power in 1933, the General Secretary of this section, Professor Rosenfeld (the same who coined the slogan, "The fats are burnt in the fire of the carbohydrates") and Professor Frank were asked to resign from membership. Professor Rosenfeld abstracted this document and, being an elderly man, gave it to Professor Frank.

Oscar Minkowski was born in Alexoten (Kowno, Russia) on January 13th, 1858, and in 1872 became a naturalized Prussian. He studied in the Gymnasium at Kowno from 1867 to 1872 and in the old Gymnasium of Königsberg. His inaugural thesis for the doctorate in medicine was accepted in 1881.

He was an assistant to Professor Naunyn in the Medical Clinic at Strassburg and later became Professor of Internal Medicine at Greifswald and afterwards at Breslau. He died in Fürstenberg (Mecklenburg) on June 18, 1931. Naunyn refers to Minkowski in his Memoirs in the following terms:

"In Minkowski I found a force of the greatest magnitude. When a student, he went back from Freiburg to his home in Königsberg, before taking the State Examination, and he asked me for a subject for his thesis. I proposed the following: Changes in the excitability of the psycho-motor cortex of the brain caused by experimental variations in the blood circulation. Perhaps the subject was the reason that no important results were obtained. In the course of this work, however, I came to appreciate Minkowski so much that when Stadelmann left I gave him the latter's position. This was a great acquisition for us, because Minkowski was a man of rare intelligence. The agility, clarity and universality of his mind, and the quickness and accuracy of his observations and opinions, endowed him with powers for exact judgment and for research in natural science. In his experimental work his great manual dexterity was very useful to him. It was surprising how easily he adapted himself to different circumstances. His elder brother, a business man of great ability, recounted to me how Oscar (my friend), when a student, frequently did his homework in his father's shop. Thus he sometimes saw samples of wheat which were passed from hand to hand. Not long after, his advice used to be asked and he would give his verdict with as much assurance and sometimes more accuracy than the experts. The removal of the liver and the removal of the pancreas were surgical achievements of the first quality, and several years passed after he had taught them before they were performed in other laboratories than my own. He had never done microscopic work; however, when we worked together on polycholic jaundice he prepared the slides and from the beginning he made them perfectly; I have never seen better sections. Already at that time we found the 'Kupfer cells,' before they were given Kupfer's name. When he was in Strassburg, a gentleman came to see me in whom I found a small polyp placed exactly on the anterior commissure of the larynx. It is very difficult to see these small tumors in this place and even more difficult to operate on them. As at that time there was nobody in Strassburg who cared to operate on this case, I asked Minkowski to do so. Minkowski, who had never even thought of operating on the larynx, laughed and would not do it. Finally, he made up his mind and practiced during a few days. About fifteen days later he told me he had 'removed the polyp completely and cleanly in one session.' 'It is not easy, but it can be done.' He was never interested in surgery; however, he was fascinated by problems. When a problem was suggested to him, with astounding acuteness he saw the decisive aspects and knew how to cope with them. Even today I 'dip my flag' to the powerful intelligence which endowed Minkowski for all this, but at times I overestimated his capacity. That spirit which pushes us into research and tortures us, and is only appeased by work done in its service, was not always alive in him and sometimes it was neccesary to stimulate it. When it awoke, Minkowski worked powerfully; otherwise, my friend could also live without an absorbing task. Ambition and the wish for official places were foreign to him. Minkowski arrived too late at a position which gave him independence and free reign to his genius. Even today I feel indignant when I think he was almost fifty years old when he obtained his first appointment. When eventually he went to Greifswald he was again passed by for many years, while places that were right for him were occupied by others. I was so annoyed by this that I decided to take a very unusual step. I sent a personal memorandum to the Prussian Minister of Education, in which I drew attention to the importance of Minkowski and to the fact that, in my opinion, this man of great worth was continually being passed over for incomprehensible reasons. I have cause to believe my request was given due attention in Berlin. In the meantime my friend found in Breslau a position worthy of him and a place where his genius could develop, but I still bear a grudge against the faculties of medicine who overlooked him for so long; my whole school suffered because its most outstanding member was forgotten. I was always having to exert my influence in favor of Minkowski to the detriment of others."

The discovery of pancreatic diabetes is usually considered as the result of chance; but luck favors those who deserve it, that is to say, those who are prepared to make use of it. The discovery was made in Naunyn's clinic, where diabetes was the main subject of study and where experimental work on problems of pathology and pharmacology was being done. A factor in this discovery was the boldness which youth sometimes brings to research, as was the case with Minkowski in 1889 and Banting in 1921. Minkowski's surgical ability and his previous training in experimental work made his achievement possible. The discovery was correctly understood from the beginning, and through many years Minkowski gave further proof of his interpretation of it by means of patient and cleverly performed experiments. He was not only an able man, he was also fair to von Mering and associated him in the publication of the results as was his due. Later both discoverers had distinguished scientific and medical careers. Undoubtedly, however, the discovery of pancreatic diabetes was due to Minkowski's determination and technical dexterity; it was he who removed the pancreas from a dog and found sugar in its urine. This experiment opened a new and fruitful era in the study of diabetes and its treatment, in metabolic research and in endocrinology.

Von Mering carried out a very distinguished scientific career; he discovered phloridzin diabetes and, in collaboration with Emil Fischer, he developed veronal. The true fact is that von Mering did not discover pancreatic diabetes nor did he do research in this field after his first publication with Minkowski.

BIBLIOGRAPHY

Frank, E.: Pathologie des Kohlehydratstoffwechsels. Benno Schwabe, Basel, 1949.

Von Mering, J., and Minkowski, O.: Diabetes mellitus nach Pankreas extirpation. Arch. f. exper. Path. u. Pharmakol. *26:* 371, 1889.

Minkowski, O.: Weitere Mitteilungen über den Diabetes mellitus nach extirpation des Pankreas. Arch. f. exper. Path. u. Pharmakol. *31:*85, 1893.

Minkowski, O.: Untersuchungen über den Diabetes mellitus nach extirpation des Pankreas. Berl. Klin. Woch. 90, 1892.

Minkowski, O.: Storungen des Pankreas als Krankheitursache. Lubarsch. Osterag's Ergebnisse der allgemeinen Aetiologie. *1:*78, 1896.

Minkowski, O.: Bemerkungen über den Pankreasdiabetes. Arch. f. exper. Path. u. Pharmakol. *53:*331, 1905.

Minkowski, O.: Ueber die Zuckerbildung im Organismus beim Pankreasdiabetes. Arch. f. d. ges. Physiol. *111:*13, 1906.

Minkowski, O.: Die Total extirpation des Duodenums. Arch. f. exper. Path. u. Pharmakol. *58:*271, 1908.

Minkowski, O.: Zur Kenntniss der Funktion des Pankreas beim Zuckerverbrauch. Arch. exper. f. Path. u. Pharmakol. Suppl. *59:*395, 1908.

Minkowski, O.: Total extirpation des Duodenums. Deutsche med. Wchnschr. 45, 1908.

Minkowski, O.: Discussion of paper of Michaud. Verhandl, d. Kong. f. inn. Med. 564, 1911.

Naunyn, B.: Erinnerungen, Gedanken und Meinungen. J. F. Bergmann, Munchen, 1925.

THE MORAL RESPONSIBILITY TO BE INTELLIGIBLE

Clinical research is predicated upon the belief that its significant results should be communicated and used by others. How miserably this is accomplished is any contemporary editor's tale of woe and any thoughtful reader's sorrow. The pseudo prestige of long and difficult words transcends the useful scientific term and diffuses widely through our papers. Simple things are made complicated and the complex is made incomprehensible. Chaos reigns. The so-called medical literature is stuffed to bursting with junk, written in a hopscotch style characterized by a Brownian movement of uncontrolled parts of speech, which seethe in restless unintelligibility. Every day we realize that the iron curtain which disbars us from sampling in adjacent fields of science is not so much the erudition of our colleagues as the tropical jungles of verbiage and gobbledegook in which this erudition lurks, unobserved save by the initiated. Has this unfortunate situation any corrective? If some small fraction of the time and effort which goes into the techniques of research were spent on study and perfection of the simple techniques of writing and speaking clearly, paths could be made in the jungle. Those who start late must read and study good models of exposition. Learn the simple rules: write, rewrite, delete, polish. For sage advice, Allbutt's "Notes on the Composition of Scientific Papers" has lost none of its cogency, and elegantly combines precept with example. For a contemporary view Gower's "Plain Words" is equally good. With such guides our scientific writing must improve. Correct grammar, thoughtfully combined with rhetoric, might lead through grace to that elusive quality, style, and make a worthy medium for telling of significant work.

—From "A Testament of Duty," by William Bennett Bean, M.D., *Journal of Laboratory and Clinical Medicine*, January 1952.

THE BEGINNINGS OF

Life Insurance for Diabetics

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Just thirty years ago, a discovery was made by two young Canadian scientists, Banting and Best, which changed the lives of thousands of people. Until 1921, when insulin was first produced, the diabetic faced an uncertain future. Insulin transformed the situation; at the present time most diabetics are able to carry on work and other activities in a normal manner.

It should be recorded that in 1918 the Sun Life Assurance Society of England issued a policy to a suspected diabetic, and in 1924 had a table of diabetic extras. However, there was some lag and it was not until 1940, nearly twenty years after the discovery of insulin, that diabetics on the North American continent had any chance of getting insurance. The late Dr. H. C. Cruikshank, then Medical Officer of the Manufacturers Life Insurance Company, decided that there must be some way in which insurance could be offered to certain diabetics. He recognized that the risk could not be assumed on all diabetics, but he felt sure that a goodly percentage did pay sufficient attention to treatment so that insurance with an extra premium could be offered them. Accordingly, in 1940 this Company advised its representatives that carefully selected diabetics would be considered for insurance. Since no company on this continent had ever before attempted such insurance, an extra premium was arbitrarily chosen—$10.00 per thousand dollars of insurance for ages 30 to 45, increased slightly each year to age 60. For a few years this Company covered the field almost single-handed, but now it is possible for a diabetic to get insurance in the United States and Canada from a great many companies, either directly or by way of reinsurance.

The original premise on which the insurance for diabetics was based was that the disorder must be well-controlled and the patient supervised by his physician. In order to obtain details regarding the situation, the

agent completed a questionnaire with the assistance of the applicant (Figure 1). The applicant was required to meet the following requirements:

1. He must have been under supervision as a diabetic for at least three years.
2. He must be on a diet.
3. The blood pressure must be normal—not over 140/90.
4. The urine must be free from sugar most of the time.
5. There must be no evidence of eye changes or peripheral vascular disease.
6. There must be a normal electrocardiogram and x-ray film of the chest.
7. The dosage of insulin, if used, must not be over 50 units per day.

FIGURE 1
DATA TO BE FURNISHED BY APPLICANT

NAME Date of Birth
RESIDENCE
1. Occupation Former occupation
2. Height Weight Weight 2 years ago
3. Date diabetes diagnosed
4. Name and address of doctor making the diagnosis
5. Are you receiving treatment or under medical supervision now? Date last seen
6. Give name and address of doctor
7. Do you ever stop insulin or go off diet?
8. Is urine sugar free? (a) Now (b) Always
Date of last test
9. Have you had any blood sugar estimations done?
10. If so, when and what were the fasting estimations?
11. What is the diet at present? Protein.....gm.
Fat.....gm. Carbohydrate.....gm.
12. Is the diet weighed or estimated? (a) Weighed
(b) Estimated
13. State amount of insulin taken daily.....units.
Time of administration
Type— Plain.....units; Protamine zinc.....
units; Globin.....units
14. Have you ever had any infections, such as boils, abscessed teeth, tonsillitis, etc.? Specify
15. Have you ever had any eye trouble?
16. Have you ever had heart trouble?
17. Have you ever had high blood pressure?
18. Have you ever had any recurring or prolonged illness?
19. Has an electrocardiogram been taken? Date
By whom (If cardiogram has been taken in the past, submit copy which will be returned.)
20. Was the electrocardiogram normal?
21. Has an x-ray of the chest been taken? Date
By whom
22. Was the x-ray normal?
23. Amount of insurance contemplated
Date Signature

FIGURE 2
DATA TO BE FURNISHED BY PHYSICIAN

NAME OF PATIENT Apparent age
RESIDENCE
1. Occupation
2. Height Weight Weight 2 years ago
Weight 5 years ago
3. Does this patient visit you regularly for supervision?
Date of last visit Date of first consultation
4. What is the diet at present? Protein.....gm.
Fat....gm. Carbohydrate....gm.
5. How is the diet measured? Weighed Estimated
6. How much insulin is taken daily?.....units.
Time of administration
Type— Plain.....units; Protamine zinc.....
units; Globin.....units
7. How much insulin was taken previously?
A year ago Two years ago
8. Has the patient had any insulin reactions?
When?
9. Does the patient follow your advice consistently?
10. Over a period of years has there been a gain or loss in tolerance?
11. Is the fasting urine free of sugar?
12. Fasting blood sugars. Give dates and estimations of recent tests.
13. Are there any changes in the eye grounds?
14. Is there any evidence of (now or in the past): Pulmonary tuberculosis? Heart disease? Any recurring or prolonged illness? Infections such as boils, infected teeth, tonsils, etc.? Any abnormality of palpable arteries?
15. Is there a good pulsation in posterior tibial and dorsal pedal arteries?
16. What is the highest blood pressure reading recorded?
17. Has an electrocardiogram been taken? Date
By whom If cardiogram taken, submit copy. (This will be returned.)
18. Was the electrocardiogram normal?
19. Has an x-ray of the chest been taken?
Date By whom
20. Was the x-ray normal?
21. Do you consider the patient a mild, moderate or severe diabetic?
22. Further comments.
Date Signature of attending physician

After obtaining satisfactory information from the diabetic, a similar questionnaire was sent to the attending physician (Figure 2) and arrangements for an examination made.

At first it was decided to grant only $10,000 insurance to any one diabetic. Gradually, as more applicants have been accepted, the amount that can be given to each individual has been increased. We will now consider $75,000 on any well-controlled diabetic.

While we have been insuring diabetics for a period of somewhat over ten years, we still feel that sufficient time has not elapsed to permit adequate evaluation of the experience with this group. The majority of policies have been in force for less than seven years. Nevertheless, a summary of certain information about policies in force, death claims, and inquiries brings out interesting information.

A survey was made of the diabetics insured in our Company up to April 1, 1951. At that time it was found that we had placed 550 policies for a total risk of $5,734,700. Of these, 76 per cent were placed in the United States, 20 per cent in Canada, and 4 per cent elsewhere.

In order to determine our experience with this group, our Actuary collected all cases insured from the beginning in 1940 up to 1949, and traced the status of each policyholder through the anniversary of each policy's issue as it fell in 1950. Only 13 deaths were found to have occurred in this group, a number too small to be considered conclusive. It should also be pointed out that the group was more heavily weighted with recent cases than is typical in our experience on other business.

Despite these two statistical abnormalities, it still is worth reporting that the mortality was between 50 per cent and 100 per cent higher than the Company average. Our basis of rating diabetics provided for 100 per cent higher than normal mortality, so that our experience to date is not seriously out of line with our original assumptions.

There may also be some value in a comparison of the number of policies actually issued with the number of inquiries received from diabetics. To arrive at this comparison, we collected all the inquiries received from diabetics from the beginning of 1950 through March 31, 1951. There were 255 in all, and they were disposed of as indicated in Table 1.

TABLE 1

Disposition of Case	Number	Per cent
Declined	106	42
Dropped	88	34
Insured:		
Ordinary extra	30	24
Additional extra	31	

The figure of 24 per cent may seem very low for the number of diabetics to whom we could offer a policy. The reasons for it are shown in Table 2.

It will be noted that the reasons for decline are essentially the same as the reasons for the charging of an additional extra premium. This is to be expected, since the same factors exist in both groups. Those given insurance upon the payment of an additional extra premium were fortunate enough to be considered only mildly abnormal; those declined were thought to be poor risks because of their abnormality. The selection of cases therefore came down to a matter of degree of abnormality.

TABLE 2

Reason for Rejection	Declined*	Additional Extra*
Lack of supervision and control	60	8
Cardiovascular disease	42	8
Renal disease	42	8
Amount of insulin	13	1
Habits	11	3
Recent diagnosis	9	3
Weight	9	6
Eye changes	7	2
Age	6	1
Other	41	3

*Most cases showed more than one impairment, and many are listed twice in this table. For this reason the totals are greater than the actual number which were declined or which were insured with additional extra premium.

We originally started out with the premise that a diabetic could not qualify if he had an impairment other than diabetes. However, in our effort to insure as many as possible in this new category, we have selected some who probably would have been declined when we first started this type of insurance. We now accept some of these if they will pay an increase over the normal extra.

It will be noted that supervision is considered an important factor in both groups. By supervision we mean the teamwork which should exist between the applicant and his doctor. Both are important players. The physician must give the patient expert advice on diet, work, exercise and general way of life. In return, the patient must not only follow his doctor's orders about his way of life, but must report at frequent stated intervals for rechecks. If either one falls down, the supervision falls down also. This teamwork involves a combined effort through which a new way of living is established for the diabetic. It influences his medical fitness, his ability to work, how he fits in with his confreres, and also his habits.

It may be that the applicant has been set on the proper path by his physician, but has decided that he can follow the rest of the way himself without further help. We do not usually insure such people, since they are in all likelihood quite unaware of their actual diabetic status. It is true that an occasional self-controlled diabetic may, by careful dieting and daily checking of the urine, remain in a well-controlled state. Indeed, many diabetics do become very proficient in looking after themselves. Even so, they are the exceptions.

In general, we want our diabetics to report for blood sugar determinations at suitable intervals, and to be in constant touch with their physicians. Actually, insufficient supervision is a matter of degree. A person who seems well-controlled may see his doctor only once a year. This is not entirely satisfactory, but it is enough—other things being equal—for us to offer him insurance at an added extra premium over what the well-controlled diabetic who sees his physician regularly is paying.

Although we feel that supervision is the most important single criterion in the selection of this group, we also recognize that if we are to offer insurance to diabetics we must be as practical and reasonable as possible. We no longer believe that it is desirable to defer a newly-diagnosed diabetic for three years before insuring him, in order to make certain that supervision is well established and that the applicant is stabilized. We have therefore reduced our waiting period for the new diabetic to one year.

Usually, applicants were either declined or offered insurance at an additional extra premium when they exhibited a *combination* of impairments. Overweight alone, however, was the major factor in a number of declinations; underweight was important in only one case. Most cardiovascular abnormalities which caused refusal to insure involved increased blood pressure. Today we accept 140/90 as the top limit of normal. Aortic calcification, electrocardiographic changes and so on played a relatively infrequent role in those given insurance with an additional extra. The overweight diabetic becomes a problem if he is 35 pounds over normal. He probably will be declined if he is 50 pounds over normal.

The persons included in the group labeled "recent diagnosis" present us with two types of problems. Certain people present new evidence which shows that they are real diabetics. We feel that these persons should wait a year before being allowed to buy insurance, so that we can make sure that they have stabilized themselves in their new way of living.

The other group included under "recent diagnosis" is composed of doubtful diabetics—people who exhibit merely a lag in the fall of the blood sugar at two hours after the beginning of the glucose tolerance test. We consider such individuals to be potential diabetics, but we are willing to insure them at once with an extra premium since, according to Joslin, only about 17 per cent become true diabetics. Furthermore, we are willing to reconsider this latter group for insurance at regular rates after a year or two.

Retinitis presents a problem. Originally we declined everyone showing changes in the retina. Currently we are being told by some that these abnormalities are not necessarily important. We are skeptical about this new viewpoint, but we sometimes do offer insurance with an additional extra premium to people with a history of retinal changes, provided that there has been no recent progression.

Renal changes are most commonly shown by albumin in the urine, which may be the first sign of degeneration. Our problem is, should we decline risks that show only a small amount of a albumin? It is, of course, essential to check these people very thoroughly for other evidence of aging; however, we do accept some if the amount of albumin is very small.

Habits alone often are decisive elements against insuring persons who otherwise are in fine physical condition. For example, we prefer diabetics who do not drink alcohol. Very light drinkers, for example, might be accepted if they definitely take only one drink. We do accept a few people who drink enough to put them just over our "normal" line; these we charge extra.

We believe that the daily dose of insulin usually gives some indication of the severity of the diabetes, though of course this will not be so with patients who are deliberately given a large caloric intake. In any event, we have felt it wise to set an upper limit to the amount of insulin a diabetic could take and still be eligible for insurance. This has currently been set at 75 units a day instead of the original 50.

At first we accepted diabetics only when they were between the ages of 30 and 60, but now we are accepting them as young as 20 years of age. It is still our feeling that the mild, recently-diagnosed diabetic who is about 45 years old will do better than one who is under 20.

It was also thought that a study of the death claims among our diabetic policyholders might teach us something, and therefore we had them analyzed. To the date of preparing this review, we have had a total of 20 claims.* The causes of death for these cases are presented in Table 3.

TABLE 3.

Causes of Death	Number
Coronary disease	11
Diabetic coma	2
Cerebral hemorrhage	2
Diverticulitis	1
Sarcoma	1
Cardiovascular renal	2
Myelogenous leukemia	1

*Including deaths occurring in the period of nearly two years following the analysis of 13 cases previously described.

Some interesting facts were uncovered during our study of these 20 claims. Diabetes varied in duration from 2 to 27 years. The ages of the deceased varied from 23 to 66. The man who was 66 had been a diabetic since he was 50. He developed diverticulitis with perforation of the sigmoid; an abscess formed; and he died of ileus.

Of the two who died of coma, one was a man of 52 who was said to have had regular blood sugar estimations. He was on a trip with his wife when he began feeling unwell and went to a hospital. The diagnosis was diabetic coma, acidosis, and general debility. This man did not take insulin, and was no doubt not well supervised. Coma should not be the cause of death in a well-controlled diabetic.

The other case of coma was that of a young man of 28. He had been a diabetic for 15 years, and took 36 units of insulin daily. He was on a fishing trip when he was found dead near a river. Some question regarding the cause of his death still remains.

Of the 11 coronary cases, satisfactory electrocardiograms existed for 7 and none for the other 4. They had the usual coronary history. One was sick only a few hours; another died during his second attack; still another was said to have had coronary sclerosis for 10 years.

One instructive case concerned a man who was 39 years old and had been a diabetic for 27 years. He was first accepted for insurance in 1945 on a high-premium plan because of the amount of insulin he had to take—70 units. The examination was quite satisfactory. The blood pressure was 128/80, the urine was negative, and the electrocardiogram and x-ray film were both normal. In 1946 he applied again. The blood pressure was the same, but there was a faint trace of albumin (less than 20 mg.) and occasional red and white blood cells in the urine. We issued a second policy, although supervision was not impressive. In 1948 this man applied again. This time his urine showed 100 mg. of albumin, the blood pressure was 156/96, there was a fast pulse rate, and low T waves in Leads I and II of the electrocardiogram were noted. We declined to insure. He died in 1950 of coronary artery disease.

One of our recent claims was that of a young man of 23 whose diagnosis had first been made when he was 14. He presented a history of coma in the past, but had had a clear history for the previous seven years. We did not have an electrocardiogram or an x-ray film of the chest. He was a very intelligent person, and we felt he was capable of good supervision. When he was examined, two specimens of urine showed 30 mg. of albumin, and the blood pressure was normal. He died five years later, when he was 28. Claim papers showed that he had developed hypertension 17 months before death, and that he died of cardiovascular disease.

Another recent claim was that of a man of 52. He was a diabetic of 2 years' standing, and was taking 50 units of insulin, although he had never had a blood sugar estimation made. He was said to have sugar-free urine. We felt that supervision could not be good, and issued a policy with a higher extra premium. The electrocardiogram and the x-ray film of the chest were both satisfactory. He died of coronary occlusion.

Our most recent death was that of a young man of 43 who died in 1951 of myelogenous leukemia. This man had been diagnosed a diabetic in 1947, and was considered a mild case. He took 12 units of insulin daily. All examinations, including an electrocardiogram and an x-ray film of the chest, were normal.

It obviously is necessary to maintain good supervision of our diabetics if we are to keep the mortality low. It is also necessary to take cognizance of all factors that indicate changes in the cardiovascular renal system. Zeal to insure diabetics must not be permitted to interfere with good judgment. Many of these people still die prematurely of cardiovascular renal disease. Consequently it seems sensible to check the cardiovascular system as carefully as possible. With this in mind we examine the applicant thoroughly, and obtain an electrocardiogram and a six-foot x-ray film of the chest if his age is 45 or over, if $10,000 or more insurance is requested, or if he has been a diabetic for 10 or more years. Similarly, as will be noted on the questionnaires, we ask both the doctor and the applicant questions concerning blood pressure, eye grounds and peripheral circulation.

In the insurance business it should in theory be possible to issue anyone a policy. (This is not true practically, because some applicants show so many signs of aging that we are unable to evaluate the risk.) Similarly, all diabetics should be insurable at a price. Yet every day we decline to offer insurance to some people in this group, because we cannot fairly measure the risk. This is, of course, unfortunate. But it should be remembered that before 1940 diabetics were unable to obtain insurance at any price. Now, of course, many companies in the United States and Canada are willing to give selected diabetics insurance. Many, of course, are unable to qualify.

The diabetic who cannot qualify for insurance very often has only himself to blame. Some diabetics, it is true, have not been diagnosed until they are in a condition which we consider uninsurable. Others, however, could be insured if they would adopt the practice of visiting their doctors at regular intervals and of following closely and continuously the advice given them.

Great strides are being made at present in the care and detection of the diabetic. Taken early, most are insurable. Physicians can do a great deal of good if they keep their patients on the proper path by insisting on constant supervision. For here is one place where supervision really pays off. The careful diabetic who knows his limitations and follows his doctor's advice will reap the benefit of the most satisfactory rate the companies can offer. The diabetic who does not bother to see his doctor, who goes off diet, who is careless regarding his insulin, will in all likelihood be penalized by having to pay a much higher premium—if he can obtain an insurance policy at all. Thus it would appear that the diabetic who obeys instructions will not only live longer and enjoy life more, but will have his insurance responsibility to his family covered, and at a cheaper rate than otherwise would be the case.

As a Company, we are interested ourselves in insuring as many diabetics as possible, but we must take only those who show the likelihood of achieving a reasonable life span. To do otherwise is to court disaster for us; it might eventually eliminate us from the business of insuring the diabetic.

CONCLUSION

1. We have insured diabetics since 1940 on an empirical basis. This seems to have been a satisfactory experience, since our mortality to date is within the limit of our estimates.
2. Our claims show that the diabetic dies primarily from cardiovascular disease.
3. The number of diabetics refused insurance is still too high.
4. We should endeavor to get all diabetics to follow consistently their physicians' advice concerning supervision and treatment.

ABSTRACTS

BARR, DAVID P. *(New York Hosp., New York City):* The relationship of endocrine factors to the development of diabetes mellitus. Smith, Kline & French Laboratories: The Clinical Problems of Advancing Years. Second Symposium, pp. 26-27, 1951.

The clinical state of diabetes mellitus is a complicated situation in which at any particular time a multitude of factors are in evidence. Many of these can be only partially evaluated, and the true nature of the disease is still in doubt. At present, diabetes appears to be due to an absolute or relative lack of insulin, which results in inhibition or diminished activation of enzymatic intracellular reactions necessary for normal carbohydrate metabolism. Excess of pituitary, adrenal, and thyroid activity may produce a state in which even a normal supply of insulin is insufficient to prevent the manifestations of diabetes mellitus.

BARR, DAVID P.; RUSS, ELLA M.; AND EDER, HOWARD A. *(Dept. of Med. of the N. Y. Hosp., Cornell Med. Center, New York City):* Protein lipid relationships in human plasma. II. In atherosclerosis and related conditions. Am. J. Med. *11*:480-93, October 1951.

The authors report the results of their studies, using the Cohn protein microfractionation method No. 10 for the separation of protein, on the plasma of 33 patients who were known or thought to be suffering from complications of atherosclerosis, 2 who exhibited advanced lesions of familial xanthoma tendinosum with hypercholesterolemia, 35 diabetics, and 12 nephrotics. Protein, cholesterol, and phospholipids were determined on the original plasma and on each of the fractions. The investigation was undertaken to determine whether there are significant abnormalities of lipid distribution in the plasma of patients with atherosclerosis or with conditions that are known to predispose to its development.

The authors conclude from their findings that patients who have survived coronary occlusion or present otherwise unequivocal evidence of the complications of atherosclerosis frequently exhibit several abnormalities in the distribution of proteins and lipids in the plasma. These include a tendency toward reduction of albumin and alpha lipoprotein, as well as other components of Cohn's Fractions I and III. These changes may be apparent without hypercholesterolemia or recognizably significant elevation of the cholesterol-phospholipid ratio of the unfractionated plasma. Like normal individuals, patients in the atherosclerotic group were found to exhibit, in the fraction containing alpha lipoproteins, cholesterol-phospholipid ratios which averaged around 0.50, and in the fraction containing beta lipoproteins, ratios which ranged about 1.40.

Similar changes in protein and cholesterol distribution were seen in conditions which are known to predispose to early and extensive atherosclerosis. The authors state that in many diabetics they are apparent before any vascular complications of the disease are clinically recognizable. They were seen in 2 cases of familial xanthoma tendinosum. They were noted to an extreme degree in patients with the nephrotic syndrome. The authors suggest that future attempts to relate lipids of the plasma to the deposition of lipids in tissue must take account of their combinations with protein; also, that further exploration of protein-lipid relationships may be rewarding both in clarifying the pathogenesis of atherosclerosis and in aiding in its early recognition.

BARTELS, E. D.; AND POULSEN, JACOB E. *(Steno Mem. Hosp., Gentofte, Denmark):* Clinical vascular symptoms in patients with juvenile diabetes mellitus after at least 15 years' duration. Rep. Steno Mem. Hosp. *4*:68-78, 1950.

One hundred and sixteen diabetics were examined fifteen years or more after the onset of diabetes. None of them was more than fifty years old at the time of examination. Vascular lesions were found in about 50 per cent (retinopathy, 27 per cent; proteinuria, 27 per cent; hypertension, 23 per cent). The mortality rate was 16.7 per cent.

BEARN, A. G.; BILLINGS, G. H.; AND SHERLOCK, S. *(Dept. of Med., Postgrad. Med. Sch., London):* Hepatic glucose output and hepatic insulin sensitivity in diabetes mellitus. Lancet *2*:698-700, October 20, 1951.

The authors employed catheterization of the hepatic vein to measure the output of glucose from the liver in 39 normal persons and 43 diabetics. Under basal conditions there is no significant difference between the hepatic glucose output in diabetics and that in normal subjects. Insulin (0.1 unit per kilogram of body weight intravenously) results in an immediate fall in the hepatic glucose output. In normal subjects this fall is fairly constant. In diabetic subjects the fall in output is variable and enables the diabetics to be divided into hepatic-sensitive and hepatic-insensitive types. In hepatic-sensitive diabetics, administration of insulin results in a greater fall than normal in the hepatic glucose output. The patients are young and thin and readily go into ketosis. Sections from aspiration biopsy of the liver show no histological abnormalities. In hepatic-insensitive diabetics, insulin results in a smaller fall than normal in the hepatic glucose output. The patients are middle-aged and obese and rarely go into ketosis. Sections from aspiration biopsy of the liver show fatty change in the liver. Hepatic-sensitive diabetics when in severe ketosis become hepatic-insensitive. Sections of liver show no remarkable histological change.

BERNSTEIN, DONALD E.; AND ENOCH, ILSE *(Mount Zion Hosp., San Francisco):* Effect of hypoglycemia on rats with intrasplenic adrenal transplants. Proc. Soc. Exper. Biol. & Med. *78*:215-17, October 1951.

The administration of alloxan to adrenalectomized rats resulted in hypoglycemic convulsions and death in two hours. This did not occur in rats with an adrenal transplanted to the portal circulation or to the peripheral circulation or when one adrenal gland was removed and the other left *in situ*. The authors conclude that the liver does not destroy the secretions of the adrenal cortex that may be concerned with carbohydrate metabolism.

BINKLEY, FRANCIS; CHRISTENSEN, GERALD M.; AND FENG, CHI WU *(Depts. of Pathology and Biological Chem., Univ. of Utah Coll. of Med., Salt Lake City):* Metabolism of glutathione. V. An effect of insulin. J. Biol. Chem. *192*:29-34, September 1951.

The authors found that the levels of glutathione in liver tissue of rats were reduced significantly following the administration of insulin. Levels of glutathione in the blood of rabbits were increased following the adminstration of insulin. The administration of glutathione to rabbits was followed by a decrease of levels of glutathione in the blood.

BLOTNER, HARRY; AND MARBLE, ALEXANDER *(Beth Israel Hosp. and New England Deaconess Hosp., Boston):* Diabetes control: Detection, public education and community aspects. New England J. Med. *245*:567-74, October 11, 1951.

This is a review article in which the following topics are discussed: The incidence of diabetes found in various diabetic surveys, the Diabetic Fair, summer camps for diabetics, life insurance for diabetics, and the role of diabetics in civil defense and in industry. The diagnosis of diabetes, including the use of different sugar tolerance tests, is described.

BORNSTEIN, J.; REID, E.; AND YOUNG, F. G. *(King's Coll. Hosp., London, and Univ. of Cambridge):* The hyperglycemic action of blood from animals treated with growth hormone. Nature *168*:903-05, November 24, 1951.

Pituitary growth hormone was given to alloxan-diabetic, hypophysectomized, adrenalectomized rats or to intact cats under conditions such that diabetes was induced. Portal blood from these animals was consistently found to exert a hyperglycemic action when administered to recipient alloxan-diabetic, hypophysectomized, adrenalectomized rats. Such a hyperglycemic effect was not found when growth hormone was administered directly to the recipient rats. These observations are consistent with

the view that under the influence of growth hormone the pancreatic islets liberate their contained hyperglycemic substance into the portal blood.

BOWEN, BYRON D.; AND LENZNER, ALFRED R. *(Univ. of Buffalo Sch. of Med., Buffalo, N. Y.):* The use of propylthiouracil in hyperthyroidism and diabetes. A study of forty-one cases. New England J. Med. 245:629-33, October 25, 1951.

During the past four years the authors have studied 41 hyperthyroid diabetics. They found that comparatively large doses of propylthiouracil were necessary to establish control of the hyperthyroid state in diabetics. A family history of diabetes was found in 55 per cent of 11 patients with hyperplastic thyroid glands and 40 per cent of 29 patients with adenomatous goiters. The most helpful clinical indication of the hyperthyroidism was failure to gain weight when there was an adequate diet and the diabetes was controlled. No change was observed in insulin need after thyroidectomy as compared with that of the controlled hyperthyroid state.

BRUGER, MAURICE; AND OPPENHEIM, ELLIOT *(New York Post-Grad. Med. Sch.):* Experimental and human arteriosclerosis: Possible relationship and present status. Bull. New York Acad. Med. 27:539-59, September 1951.

Atherosclerosis, a form of arteriosclerosis, is a disorder which is associated with deposition of lipids in the intima and which involves the aorta and its visceral branches as well as the coronary and cerebral arteries. Atherosclerosis is not the exclusive stigma of age. A high incidence of the disease has been reported in men under 35 years of age in the American Army, and it has also occurred in children 16 years of age or younger.

Cholesterol plays an important part in the etiology of atherosclerosis. Human atherosclerosis is prominent in those clinical states accompanied by hypercholesteremia, e.g., diabetes mellitus, myxedema, nephrosis, familial hyperlipemia, primary xanthomatosis, etc.

Atherosclerosis did not develop in rabbits with alloxan diabetes, although they exhibited gross lipemia, even on forced feeding of cholesterol.

In the obese the incidence of atherosclerosis is twice as high as in the poorly nourished. Resorption of previously formed atheromatous lesions may occur during periods of marked weight loss. Prolonged consumption of foods low in fat and free of cholesterol may inhibit cholesterol deposition.

CAMPBELL, JAMES; LEI, H. P.; AND DAVIDSON, L. W. F. *(Univ. of Toronto):* Production of diabetes and increased erythrocyte sedimentation rate by purified growth hormone. Endocrinology 49:635-46, November 1951.

The administration of adequate doses of a crystalline growth hormone to fed dogs causes a progressive and marked increase in the rate of sedimentation of erythrocytes. The volume per cent of erythrocytes is usually decreased, but this cannot wholly account for the effect on the sedimentation rate. There is also a suggestion that the total protein and fibrin of the blood plasma increase. These changes coincide with, and follow fairly closely, the hyperglycemia and glycosuria produced during the administration of the growth-hormone preparation. Such great changes in the sedimentation rate, however, were not found during the subsequent metahypophyseal (permanent pituitary) diabetes produced in one of these dogs by growth hormone. In an alloxan-diabetic dog the sedimentation rate was normal; in several depancreatized dogs, it was elevated but not nearly to the same extent as by the administration of growth hormone. Thus it appears that hyperglycemia from various causes is not always accompanied by a rise in the sedimentation rate. Although these two effects were elicited by growth hormone, it cannot of course be concluded from these experiments that they are necessarily related.

COCHRANE, HERBERT A.; AND GROSS, LUDWIG *(Dept. of Med., St. Vincent's Hosp., Staten Island):* Medical problems in diabetic surgery. New York State J. Med. 51:2403-06, October 15, 1951.

The authors discuss the evaluation of the surgical risk of diabetic patients from the physiopathologic standpoint. A program is outlined for preoperative and postoperative management, which includes frequent feedings and multiple doses of unmodified insulin. Sixty diabetic cases referred to surgery are analyzed. The patients are divided into two groups. In the first group (25 patients), which was not evaluated and treated according to the principles outlined, 4 patients (or 16 per cent) expired following surgery, apparently because of cardiovascular complications. In the second group (35 cases) there was one death (or 2.8 per cent) due to uncontrollable sepsis, in spite of the fact that the average age of the patients in the second group was raised five years. The trend toward lumbar sympathectomy in arteriosclerotic occlusive disease is discussed.

COHEN, MAURICE: The place of heredity in the etiology of diabetes in Tunisia. Presse méd. 59:855, June 16, 1951.

Heredity of diabetes in Tunisia amounts to 35 per cent. This is a high figure, probably lower than the true state but more probably in proportion to the alimentary customs of the country.

COLLAZO, JUAN A. *(Montevideo, Uruguay):* A new hypoglycemia: 6. Hypoglycemic effect of tetraethylammonium in diabetic patients. An. Fac. de med. de Montevideo 35:1315-22, October-November-December 1950.

Tetraethylammonium simultaneously reduces the glucose and lactic acid content of the blood in a constant and noticeable manner. Often it interferes with the increase in the blood sugar and lactic acid brought about by the injection of glucose or by the injection of adrenalin. In cases of diabetes untreated with insulin, it reduces the blood sugar and the lactic acid content of the blood as well as the blood pressure as measured thirty minutes later.

COLLAZO, JUAN A. *(Montevideo, Uruguay):* Diabetes veratrinica: Hyperglycemia, hyperlactacidemia, and hyperpotassemia. An. Fac. de med. de Montevideo 35:1323-66, October-November-December 1950.

The use of veratrin sulfate in laboratory animals (dog, rabbit, and rat) causes the following changes in carbohydrate metabolism: (a) hyperglycemia, (b) hyperlactacidemia, (c) hyperpotassemia. Prolonged contractions due to veratrin are always accompanied by these changes. Veratrin shock brings about the death of the animals because of a tremendous increase in plasma potassium.

CRAMER, HARRY I. *(Montreal, Quebec):* Diabetes mellitus and pregnancy. Canad. M. A. J. 65:328-33, October 1951.

A series of 84 pregnancies in 73 diabetics is presented and analyzed. The maternal survival was 100 per cent and the fetal mortality, 30 per cent; multiparae showed a higher mortality than primiparae. Although the age of the mother showed no effect on the fetal mortality rate, long duration of diabetes increased it. Juvenile diabetics showed a very high mortality rate. Severe diabetics showed a higher rate than mild diabetics. All cases of diabetic acidosis terminated in death of the fetus. There was no relationship between level of serum prolan and fetal mortality, nor between signs of toxemia and the fetal death rate. A series of multiparae in whom one or more previous pregnancies had resulted in fetal death showed no higher death rate than other multiparae. Cases submitted to cesarean section showed a low fetal mortality rate (8 per cent). There was no difference in the average weights of live and dead fetuses born at the same period of the pregnancy. Poor diabetic treatment and toxemia of pregnancy resulted in greater average fetal weight. Also presented is a series of 16 fetuses weighing over 4,000 gm. and born two to fifteen years prior to the onset of the diabetes in the mother.

DEZOYSA, V. P. *(Gen. Hosp., Colombo, Ceylon):* Clinical variations of the diabetic syndrome in a tropical country (Ceylon). Arch. Int. Med. 88:812-18, December 1951.

Diabetes in Ceylon presents several important clinical characteristics, namely, mildness of the disease and low incidence of acidosis and coma, peripheral vascular occlusive disease, and obesity. These features are held to be due to the dietary habits of the people. The people of Ceylon consume a diet containing a higher proportion of carbohydrate (70 per cent) and a lower proportion of fat (17.5 per cent) than those of most Western countries. The low fat intake is reflected in the low incidence of obesity among the diabetics. The absence of hypercholesteremia, the low fat intake in food, and the low incidence of obesity and hypertension probably constitute several of the factors which reduce the incidence of arteriosclerotic occlusive disease.

DIERMEIER, H. F.; DISTEFANA, H. S.; TEPPERMAN, J.; AND BASS, A. D. *(State Univ. of N. Y. Coll. of Med., Syracuse):* Effect of alloxan administration on liver nucleoproteins. Proc. Soc. Exper. Biol. & Med. 77:769-71, August 1951.

Administration of alloxan to white rats caused an increase in the desoxyribose nucleic acid (DNA) on the following fourth, fifth, and sixth days. Direct measurements indicated no change in cytoplasmic ribose nucleic acid (RNA), but indirect evidence suggested an increase in nuclear RNA. The DNA increase could not be correlated directly with the blood-sugar levels.

DUNCAN, GARFIELD G.; AND BEIDLEMAN, BARKLEY *(Jefferson Med. Coll., Pennsylvania Hosp., and Benjamin*

Franklin Clin., Philadelphia): Diagnosis of diabetes mellitus, diabetic coma, and some of its chronic complications. M. Clin. North America (Philadelphia Number) 1607-19, November 1951.

The early diagnosis of diabetes is stressed. Emphasis is placed on the postprandial blood sugar curve after a test meal of 100 gm. of carbohydrate. The indications for the oral glucose tolerance test and the intravenous glucose tolerance test are likewise given.

Diabetic coma may be diagnosed in the home when a 4 plus reaction for sugar, acetone in the urine, and a 4 plus reaction for acetone in the plasma of a diabetic patient are found. Such findings establish the diagnosis and permit the early initiation of insulin therapy.

Chronic complications of diabetes occurring in the eyes and coronary arteries and also diabetic neuropathies are discussed at length. The means by which these degenerative disorders may be detected are outlined.

DURY, ABRAHAM *(Bradford, Penn.):* The effect of epinephrine and insulin on the plasma potassium level. Endocrinology *49*:663-70, November 1951.

Epinephrine (0.02 mg./100 gm. of rat, subcutaneously) was shown to induce a significant fall in the mean level of plasma potassium in normal intact, adrenalectomized, adrenal-enucleated, and hypophysectomized groups of rats 60 minutes after injection. There was no change in the level of plasma potassium in normal or adrenalectomized groups of rats 180 minutes after epinephrine injection. Insulin (0.5 unit/rat, subcutaneously) induced a significant fall in the mean plasma potassium level in normal intact rats 60 minutes after its injection but did not affect the plasma potassium in the groups of adrenalectomized or adrenal-enucleated rats, nor did insulin affect the plasma potassium in any of these groups of rats 180 minutes after its injection. Evidence is presented that epinephrine as such should be considered as having an integral role in potassium homeostasis which does not involve the anterior pituitary-adrenocortical axis. The effect of insulin on the level of plasma potassium in normal intact rats is shown to be mediated by "reflex" stimulation of the adrenal medulla. Data were presented showing that the level of blood glucose per se did not affect the plasma potassium level.

EDELMAN, J.; AND BACON, J. S. D. *(Dept. of Biochemistry, Univ. of Sheffield, Sheffield, England):* The action of a hydrolytic enzyme system from Helianthus tuberosus L. on carbohydrates present in the tubers. Biochem. J. *49*:446-53, September 1951.

The authors have demonstrated that aqueous extracts of tubers of the Jerusalem artichoke *(Helianthus tuberosus)* show, on incubation, an increase in reducing substances and a decrease in optical rotation. The enzyme or enzymes responsible have been freed from the tuber carbohydrates and concentrated twentyfold by fractional precipitation with ammonium sulfate. By the use of paper partition chromatography, such preparations have been shown to liberate fructose from various substances, including sucrose, inulin, a levan, and irisin 'B'; glucose was detected among the hydrolysis products of inulin. The liberation of reducing sugars from the tuber carbohydrates and from inulin virtually ceased before complete hydrolysis had taken place. The residual combined sugar was in the form of a disaccharide, probably sucrose. From these observations, the main hydrolytic activity of tuber preparations has been characterized as that of a fructofuranosidase, with a moderate degree of specificity for such residues linked to position 1 of another fructose residue.

EDELMAN, J.; AND BACON, J. S. D. *(Dept. of Biochemistry, Univ. of Sheffield, Sheffield, England):* Transfructosidation in extracts of the tubers of Helianthus tuberosus L. Biochem. J. *49*:529-40, September 1951.

The authors have obtained enzyme preparations from artichoke tubers which catalyze the transference of fructose residues from inulin and associated polysaccharides to sucrose, thereby forming a trisaccharide and higher oligosaccharides. Evidence has also been obtained for the transference of fructose residues to raffinose, melezitose, and free fructose but not to maltose, lactose, trehalose, or glucose. The liberation of free hexose which took place in all the preparations examined does not appear to be connected quantitatively with the group-transfer reaction. The reaction, for which the name "transfructosidation" is proposed, is discussed in the light of existing knowledge of hydrolytic and group-transferring enzyme systems.

EDITORIAL *(Arizona Med. Asso., Phoenix):* Lost—one million. Arizona Med. 8:51-52, October 1951.

It is estimated that there are one million undiagnosed diabetics in the United States. This is approximately 1 out of every 150 individuals. It is primarily the responsibility of the medical profession to find these persons

before they are crippled and their lives are destroyed by this chronic, destructive disease.

Diabetes Week has been set aside as a time to put forth concentrated special effort to find the unknown cases of diabetes. This Drive, sponsored by the American Diabetes Association, is unique in that it is not a fund-raising campaign.

EDITORIAL *(England):* Diabetes and growth. Brit. M. J. 2:1202-03, November 17, 1951.

The subject of experimental diabetes is discussed, with special reference to the role of the pituitary in the production of the diabetic state. Though human diabetes has suggestive affinities with the experimentally produced diabetes of animals, it is clear that pituitary overactivity by itself fails to explain much that is mysterious in diabetes and cannot be regarded as the only factor of importance in the human disorder. It would appear that the abnormal demands for increased insulin secretion, whether coming from the anterior pituitary gland or elsewhere, can be met by the pancreas of the majority of normal individuals and that an inadequate pancreatic response is at least as important in determining the development of diabetes as the nature of the diabetogenic stimulus.

EDITORIAL (*England*): Diabetic nephropathy. Lancet 2:974, November 24, 1951.

The subject of renal lesions in diabetes is discussed. It is pointed out that the renal changes associated with diabetes include acute and chronic pyelonephritis, arteriosclerosis and arteriolosclerosis, and fatty degeneration of the tubules, as well as intercapillary glomerulosclerosis. Since it is common to discover, at post-mortem, more than one of these entities in diabetics with renal disease, the more descriptive term of diabetic nephropathy has been suggested. The clinical course of such patients is reviewed. The probable relationship of poor control of the diabetic state to the development of such degenerative lesions is discussed.

EDITORIAL *(England):* Two types of diabetes. Lancet 2:722-23, October 20, 1951.

Note is made of the two clinical types of diabetics. One type is described as the young, thin type with marked insulin sensitivity, a tendency toward ketosis, and usually with healthy arteries, kidneys, and eyes; the other, as the middle-aged, obese type, with vascular, renal, and ocular complications but with no great tendency toward ketosis and relative insensitivity to insulin. Recently, blood insulin assays have shown that the former type has no demonstrable insulin in the blood, whereas it is present in the latter type. Still more recently it has been shown, by hepatic vein catheterization in normal and diabetic persons, that the fasting hepatic glucose outputs in these two groups are approximately the same. When insulin is given, the hepatic glucose uptake is above normal range in the insulin-sensitive diabetics, and liver biopsy reveals fatty change. In the insulin-insensitive patients the hepatic glucose uptake after insulin is subnormal, and normal liver biopsies are found. These findings are more in line with the underutilization theory than with the overproduction theory. Various facets of this problem are discussed briefly.

ENGEL, FRANK L. *(Depts. of Med. and Physiol., Duke Univ., Durham, N.C.):* Observations on the interrelationship between insulin, the adrenal cortex and non-specific stress (cold) in adipose tissue glycogen synthesis in the rat. Endocrinology 49:127-35, July 1951.

The concentration of glycogen in the interscapular adipose tissue of fasted, adrenalectomized rats maintained on a constant dose of cortisone and receiving a fixed amount of glucose by stomach tube increased in direct proportion to the logarithm of the dose of insulin. Blood-sugar and liver glycogen concentrations decreased with increasing doses of insulin. The concentration of glycogen in the interscapular adipose tissue of fasted, adrenalectomized rats receiving a constant dose of insulin and glucose was not influenced by the amount of cortisone administered. Liver glycogen and blood-sugar levels increased with the dose of cortisone.

Exposure of normal, fasted rats to 4°C. for 48 hours had no influence on the levels of interscapular adipose tissue and liver glycogen or blood sugar after administration of glucose. However, insulin stimulated a striking increase in the glycogen concentration of the interscapular adipose tissue of the cold-stressed rats as compared with control animals at room temperature. Blood-sugar levels were lower after insulin in rats exposed to cold. Cortisone-maintained, adrenalectomized rats exposed to 4°C. for 24 hours did not show any

modification of the concentration of glycogen in interscapular adipose tissue after insulin and glucose compared with similar animals kept at room temperature. Liver glycogen and blood-sugar levels were significantly lower in the cold-stressed, cortisone-maintained, adrenalectomized rats given insulin and glucose. It was concluded that among those studied, insulin is the most important variable in determining the concentration of glycogen in adipose tissue. Possible mechanisms for the alterations in adipose tissue glycogen by insulin and adrenal cortical hormone are considered.

EPSTEIN, SAMUEL H. *(Dept. of Neurology, Harvard Med. Sch., and Neurological Unit, Boston City Hosp., Boston):* Diabetic neuropathy and its prognosis. Neurology *1*:228-35, May-June 1951.

Diabetic neuropathy is best classified from the prognostic point of view into two types: (1) cases associated with arteriosclerosis, and (2) cases without demonstrable evidence of vascular disease. The latter type indicates a good prognosis, whereas the prognosis is distinctly poor in the former. There is little if any improvement in cases in which arteriosclerosis is present, and usually there is progression of the symptomatology. The age of patients without arteriosclerosis is usually under forty years, in contrast with the older age of those whose diabetes is associated with arteriosclerosis. Poor control of diabetes in either group plays a role in the precipitation or aggravation of neuropathy.

ERMALA, PENTTI; HOESTI, LARS R.; AND SETALA, KAI *(Dept. of Anatomy and Second Med. Clin., Univ. of Helsinki, Finland):* Lipomicronemia in mice caused by parenteral administration of fat. Am. J. M. Sc. 222:436-39, October 1951.

Parenterally administered fats enter the blood stream in the form of visible small particles, so-called lipomicrons, the physical state of which most probably is similar to that of the alimentary chylomicrons. A preceding emulsification of the fat is necessary before it is carried by the blood as visible particles. Spontaneous emulsification may occur also under normal conditions. The possible absorption mechanism is briefly discussed.

EVANS, MARGARET A.; AND HAIST, R. E. *(Dept. of Physiol., Univ. of Toronto):* Effect of administration of relatively large amounts of insulin on growth of the islets of Langerhans. Am. J. Physiol. *167*:176-81, October 1951.

The daily injection of relatively large amounts of insulin led to a reduction in the rate of growth of the islets of Langerhans in the pancreas of rats. This treatment did not affect the growth of the pancreas or lead to a reduction in the islet weights below the initial values.

FAIRBRIDGE, R. A.; WILLIS, K. J.; AND BOOTH, R. G. *(Bovril Res. Lab., Old Street, London):* The direct colorimetric estimation of reducing sugars and other reducing substances with tetrazolium salts. Biochem. J. 49:423-27, September 1951.

The authors studied the reaction between triphenyltetrazolium bromide and various reducing agents. Conditions for optimal production of triphenylformazan by this reaction were established. Triphenylformazan has been prepared, and its absorption and solubility characteristics have been determined. Direct colorimetric methods, based on the use of tetrazolium, are described for the estimation of blood sugar, glucose, lactose, cysteine, and ascorbic acid.

FARBER, S. J.; PELLEGRINO, E. D.; CONAN, N. J.; AND EARLE, D. P. *(Dept. of Med., New York Univ. Coll. of Med.):* Observations on the plasma potassium level of man. Am. J. M. Sc. *221*:678-87, June 1951.

The fasting venous plasma potassium level in 70 normal subjects was 4.4 mEq per liter.

The venous plasma potassium level was not affected by stasis but was increased transiently by even slight exercise in veins draining the exercising muscles.

Under fasting conditions, arterial and venous plasma contained the same amount of potassium with but rare exceptions.

Plasma potassium levels were low in alkalosis and advanced hepatic failure, normal in diabetics not in acidosis and in congestive heart failure, and frequently increased in patients with renal disease whose glomerular filtration rates were less than half of normal.

Plasma potassium level was reduced by glucose loading in normal but not in diabetic subjects. Insulin reduced plasma potassium in all subjects. Inorganic phosphate behaved similarly, except that it did decrease slightly in the diabetics during glucose loading.

Venous plasma contained more potassium than did arterial plasma during glucose loading and insulin administration and despite falling arterial plasma potassium levels. Differences did not develop in inorganic phosphate levels of arteriovenous plasma. This suggests that under these circumstances potassium is being localized at a rapid rate in certain organs, especially the liver, and that in an effort to maintain the plasma level, potassium is contributed by the peripheral tissues.

FAZEKAS, JOSEPH F.; ALMAN, RALPH W.; AND PARRISH, ALVIN E. *(Georgetown and George Washington Med. Serv. of Gallinger Mun. Hosp., Washington, D. C.):* Irreversible posthypoglycemic coma. Am. J. M. Sc. 222:640-43, December 1951.

Cerebral hemodynamics and oxygen utilization were studied at intervals in four patients with irreversible posthypoglycemic coma who respectively survived three days and one, two, and three weeks. The cerebral metabolic rate was moderately to markedly reduced in all subjects, and in three cases it continued to decrease, eventually reaching extremely low levels. The mean cerebral blood flow showed a marked reduction in only one subject, although in two others a progressive reduction in flow and increase in cerebral vascular resistance were noted. The markedly low rates of cerebral oxygen consumption finally observed must be attributed to impairment of enzymatic activity.

FELTS, J. M.; CHAIKOFF, I. L.; AND OSBORN, M. J. *(Div. of Physiol. of the Univ. of California Sch. of Med., Berkeley):* Insulin and the fate of lactate in the diabetic liver. J. Biol. Chem. 191:683-92, August 1951.

The investigation deals with the action of insulin at the bridge between glycolysis and the oxidative cycle. The metabolism of lactate -1-C^{14}, lactate -2-C^{14}, lactate -3-C^{14}, and acetate, in which both carbons were labeled with C^{14}, was studied in surviving liver slices prepared from (1) normal rats, (2) alloxan-diabetic rats, and (3) alloxan-diabetic rats that had received insulin for several days before their sacrifice.

About 2 per cent of the *a* and β carbons of lactate were found to be incorporated into fatty acids by the normal liver. Practically none of the carboxyl carbon was incorporated into fatty acids. From 30 to 60 per cent of the carboxyl carbon was converted to CO_2, and no significant differences were observed in the amounts so converted in the three experimental states cited. The influence of insulin on the formation of C-2 fragments derived from lactate and other sources is discussed. In the case of each liver, regardless of experimental state, the amounts of the *a* carbon converted to CO_2 were about twice those observed for the β carbon. One per cent or less of the added *a* and β carbons of lactate was incorporated into fatty acids by the diabetic livers. Previous insulin injections resulted in a hundredfold increase in the recoveries of the *a* and β carbons as fatty acids and a pronounced reduction in their amounts converted to CO_2. The authors suggest that at the point in carbohydrate utilization at which lactate enters, insulin shifts reactions from oxidation to synthesis.

FUHRMAN, FREDERICK A. *(Dept. of Physiol., Stanford Univ. Sch. of Med., Palo Alto, Calif.):* Glycogen, glucose tolerance and tissue metabolism in potassium-deficient rats. Am. J. Physiol. 167:314-20, November 1951.

In experiments on male rats pair-fed for eight days on a potassium-deficient or control diet, effecting by the former diet a 40 per cent reduction in muscle potassium, the following observations were made on the two sets of animals:

1. No significant difference in the fasting blood glucose concentration.
2. A reduced glucose tolerance after intravenous injection but not after oral administration in the potassium-deficient animals.
3. Greater weight of the adrenals and atrophy of the thymus in the deficient animals.
4. Higher liver glycogen in fasting deficient animals, perhaps due to increased gluconeogenesis resulting from an enhanced production of 11-oxysteroids. Nonfasting control animals exhibited higher liver glycogen.
5. No evidence of inhibition of oxygen consumption in liver, cerebral cortex, kidney cortex, skeletal muscle, or diaphragm as the result of potassium deficiency.
6. Slightly greater anaerobic glycolysis of diaphragm in potassium-free medium in potassium-deficient animals.

GATES, EDWIN W. *(Mt. St. Mary's Hosp. and Niagara Falls Mem. Hosp.):* The general medical care of the diabetic. New York State J. Med. 51:2353-55, October 15, 1951.

Some important practical aspects in the general medical care of the diabetic are discussed.

GITMAN, LEO; LEVINE, ELLIOT A.; APPELMAN, DAVID H.; AND JACOBI, MENDEL *(Endocrine Lab., Dept. of Labs. and Med., Beth-El Hosp., Brooklyn):* Effect of insulin and glucose in chronic lymphatic leukemia. New York State J. Med. *51*:2257-59, October 1, 1951.

The effect of insulin and glucose on the lymphocyte count in a case of chronic lymphatic leukemia was investigated. Insulin given intravenously produced a triphasic pattern of changes in the lymphoctye levels. A prompt initial fall was noted. This was followed by a sharp rise and again a sharp decrease which persisted for at least twenty-four hours. Administration of glucose produced a further decrease. The theoretic considerations are discussed.

GRAHAM, DEAN M.; LYON, THOMAS P.; GOFMAN, JOHN W.; JONES, HARDIN B.; YANKLEY, ALEXANDER; SIMONTON, JOHN; AND WHITE, SIDNEY *(Donner Lab., Div. of Med. Physics and the Radiation Lab., Univ. of Calif., Berkeley):* Blood lipids and human atherosclerosis: The influence of heparin upon lipoprotein metabolism. Circulation *4*:666-73, November 1951.

Heparin administered to humans and rabbits causes profound reorientation in the distribution of low-density lipoproteins; this is characterized by a shift of lipoproteins of high Sf rates to those of successively lower Sf rates. The observations appear to indicate that this agent has actually caused a transformation of the former group into the latter. Heparin administered to the rabbit prevents the usual buildup of high concentration of the Sf 10-50 lipoproteins during cholesterol feeding and retards the development of atherosclerosis. In man, accompanying the redistribution of lipoproteins, a marked reduction in angina pectoris was observed in 55 of 59 patients studied who presented this symptom. The relationship between the heparin effect upon lipoproteins and upon angina cannot be assessed at present.

GRAYZEL, HAROLD G.; AND WARSHALL, HYMAN B. *(Pediat. Dept., Jewish Hosp., Brooklyn):* Clinical survey of vascular complications in "juvenile diabetes mellitus." Pediatrics *8*:506-12, October 1951.

In a series of 25 cases of juvenile diabetes, none of the patients whose control was considered good developed detectable vascular lesions even though they had the disease for ten to twenty-eight years. This survey adds to the slowly accumulating clinical data indicating decided benefits of a well-controlled diabetic state in humans.

GRIER, ROBERT M.; AND NEWCOMB, ALVAH L. *(Northwestern Univ. Med. Sch., Chicago):* The management of pregnancy and the newborn infant of diabetic mothers. Quart. Bull. Northwestern Univ. M. School *25*:268-69, Fall 1951.

The principles of the management of the newborn infants of diabetic mothers are discussed. If the pregnancy can be successfully carried to the thirty-sixth or, better, to the thirty-eighth week, the great majority of these infants ought to survive, particularly if sedation and general anesthesia are avoided, gastric suction is immediately employed, and delayed clamping of the cord is carried out. Oxygen is essential for the first few days. Glucose feeding should be prescribed if indicated.

GRUNERT, R. R.; AND PHILLIPS, PAUL H. *(Dept. of Biochem., Coll. of Agr., Univ. of Wisconsin, Madison):* The inability of liver homogenates to convert uric acid to alloxan. J. Biol. Chem. *191*:633-38, August 1951.

The demonstration that uric acid is diabetogenic only in methionine-deficient animals suggested to the authors that a lack of sulphydryl groups might result in the abnormal formation of alloxan from uric acid. Accordingly, the effect of sulphydryl inhibitors on the conversion of uric acid to allantoin was studied. The results showed that sulphydryl inhibitors did not effect the conversion of uric acid to allantoin by rat liver homogenates in vitro, despite the variable inhibition of uric acid oxidation. Liver homogenates from methionine-deficient rats permitted the quantitative conversion of uric acid to allantoin. Alloxan, or dialuric acid, and urea did not condense to form uric acid in the presence of glutathione. The quantitative conversion of uric acid to allantoin by sulphydryl-low liver homogenates from methionine-deficient rats and the inability of sulphydryl inhibitors (with a few exceptions) to disrupt the conversion suggest to the authors that uric acid cannot be considered a source of alloxan in the animal body.

HACKEDORN, H. M. *(Mason Clin., Seattle):* Some aspects of carbohydrate chemistry. Bull. Mason Clin. *5*:105-11, December 1951.

The enzyme systems responsible for the metabolism of carbohydrate are presented. There is a brief discussion of the respective roles of insulin, other hormones, and vitamins in these enzyme systems.

HALL, ROBERT E.; AND TILLMAN, ALVIN J. B. *(Sloane Hosp. for Women and Dept. of Obst. and Gynec., Coll. of Physicians and Surgeons, Columbia Univ.):* Diabetes in pregnancy. Am. J. Obst. & Gynec. *61*:1107-15, January-June 1951.

An analysis is presented of cases of diabetes in pregnancy (112 patients, 147 pregnancies) at Sloane Hospital since the advent of insulin therapy. Diabetes was found in 1 out of every 480 pregnancies. One maternal death occurred in a patient with severe hypertension. In the authors' experience, the most vital prerequisites to successful outcome are early diagnosis and meticulous supervision of diabetes. Changes in glucose tolerance may be sudden or insidious; unrecognized or inadequate therapy of these conditions may result in fetal death. With the exception of 12 early spontaneous and 28 therapeutic abortions, gross fetal mortality was 20.7 per cent. Further exclusion of 3 late abortions reduced it to 18.3 per cent among 104 viable births. In an analysis of causes of fetal loss, inadequate antenatal care was thought to be the factor most often responsible; exclusion of inadequately treated cases would lower the mortality to 7.6 per cent of viable births. Acidosis alone killed the fetus in 6 cases. Toxemia observed in 32 per cent of the patients was associated with 8 fetal fatalities but was regarded as the sole cause of death in only 3 of them. Two of these occurred in patients who were severe juvenile diabetics. Premature delivery was also found to play a role in fetal mortality, especially in cases with poor diabetic control. Big babies were a minor factor; hydramnios, congenital defects, and abortions per se were thought to be of negligible significance. Sixteen per cent of the patients underwent cesarean section. Although this means of delivery was considered more freely in cases of previous stillbirth or refractory toxemia, its routine use is thought to result in more neonatal deaths than fetuses saved from death in utero. Induction of labor is recommended. Sterilization and therapeutic abortion serve a distinct, though circumscribed, function in the management of these cases.

HAMWI, G. J.; AND VON HAAM, E. *(Depts. of Med. and Pathol., Ohio State Univ., Columbus):* The differential diagnosis of hyperglycemic states by laboratory methods. Am. J. Clin. Path. *21*:701-10, August 1951.

In 23 subjects in whom a disturbance of carbohydrate metabolism was suspected, the glucose tolerance and the insulin-glucose tolerance were studied in conjunction with other supplementary laboratory tests. Decreased insulin sensitivity was recognized by the insulin-glucose tolerance test. It was taken as evidence of the presence of extrapancreatic factors influencing the carbohydrate metabolism. With these criteria, 7 of the 23 subjects were recognized as having normal carbohydrate metabolism, leaving 16 with hyperglycemia. The latter were classified into four groups: 4 with true pancreatic deficiency, 4 with hyperglycemia caused by extrapancreatic factors, 3 with hyperglycemia showing pancreatic deficiency and extrapancreatic factors, and 5 with hyperglycemia with insulin effect and insulin sensitivity. The hypothesis is presented that a patient suffering from a disturbance in carbohydrate metabolism may change from one group to another, thereby either aggravating or improving the state of his hyperglycemia.

HANSEN, R. G.; RUTTER, WILLIAM J.; AND SAMUELS, LEO T. *(Dept. of Biochem., Univ. of Utah Coll. of Med., Salt Lake City):* The effect of previous diet on the metabolism of glucose by rat diaphragm. J. Biol. Chem. *192*:243-49, September 1951.

The initial glycogen content of the muscle was found to have a marked effect on the glucose uptake and glycogen change of the diaphragm in a glucose medium. Glucose uptake by the isolated rat diaphragm was greater in both fed and fasted rats which had received a high-carbohydrate diet than in similar rats fed a high-fat diet. The decreased glucose uptake, coupled with an increased lactate and pyruvate formation, suggested to the authors a noncarbohydrate oxidative preference by the isolated diaphragm from animals fed a fat diet. An insulin stimulation proportionate to the original glucose and glycogen change was observed in the tissue from all animals independently of diet.

The authors conclude from their results that previous carbohydrate feeding favors uptake of glucose and metabolism of lactic and pyruvic acids by the isolated diaphragm, whereas previous feeding of a high-fat diet inhibits these effects.

HARPER, R. M. J. *(Barnstaple, England):* Coma due to acidosis. Brit. M. J. *2*:909, October 13, 1951.

The author reports the case of a young boy with coma due to acidosis which was not diabetic in origin.

HERAPATH, J. C. *(Salford Royal Hosp., England):* Diabetic intermittent claudication. Lancet 2:595-96, September 29, 1951.

The author describes an elderly female diabetic with intermittent claudication and hypertension, with no evidence of neuropathy or arteriosclerosis. Careful regulation of her diabetes resulted in marked amelioration of her symptoms. Comment is made on the comparative rarity of complete relief from symptoms without surgical intervention.

HILDRETH, E. A.; HILDRETH, B. S.; AND MELLINKOFF, S. M. *(Dept. of Therapeutic Res. and the Dept. of Med., Hosp. of the Univ. of Pennsylvania, Philadelphia):* Principles of a low fat diet. Circulation 4:899-904, December 1951.

From personal experience on low-fat diets and through experience gained by treating patients with low-fat diets, the authors suggest that when such a diet is prescribed carefully it may be quite palatable and also may reduce serum cholesterol concentration. The principles of a low-fat diet and methods for making the diet appetizing are presented. Sample diet instruction sheets which can be individualized for different patients are also illustrated. The point is made that the total fat content of the diet is a more important factor in determining serum cholesterol concentration than is the amount of cholesterol ingested.

JARLOV, NIELS V. *(Steno Mem. Hosp., Gentofte, Denmark):* Insulin allergy and insulin resistance. Rep. Steno Mem. Hosp. 4:79-85, 1950.

Now that purified preparations are used, allergic reactions to insulin rarely occur. Two types of reaction are seen: the local and the constitutional. The latter is very rarely observed. Insulin resistance may or may not be associated with allergy to insulin; when association occurs, these two conditions appear and disappear simultaneously. Four cases are presented to illustrate association or lack of association of the two conditions. The possibility of a genuine insulin allergy is discussed in conection with insulin resistance, but the author believes that most allergic responses are produced by impurities.

JOHNSON, G. R. A.; SCHOLES, GEORGE; AND WEISS, JOSEPH *(Univ. of Durham, King's Coll., Newcastle upon Tyne, England)*: Formation of *a*-keto acids from *a*-amino acids by the action of free radicals in aqueous solution. Science *114*:412-13, October 19, 1951.

In a study of the mechanisms of metabolic processes, the authors report in-vitro experiments demonstrating the formation of *a*-keto acids from various amino acids (alanine, serine, and leucine) after the production of the free radicals OH and HO_2 by chemical decomposition of H_2O_2 and by x-ray irradiation of dilute solutions.

KNAPP, ROBERT G., JR.; NATHANSON, IRVING G.; AND MALLETT, STEPHEN P. *(Boston):* Acute dental infection in diabetes: Report of a case. Oral Surg., Oral Med. & Oral Path. 4:1369-74, November 1951.

The prevention of infection following dental procedures depends on adequate control, aseptic technic, and proper prophylactic antibiotic therapy when indicated. The management of coexisting diabetes and acute infection is closely interrelated. A case report is presented of cellulitis of the neck and floor of the mouth in a previously undiagnosed mild diabetic following operative dental treatment.

KRAFT, IRVIN A.; SALZBERG, HERBERT; AND ROSENKRANTZ, J. A. *(Neuropsychiatric and Med. Services, Veterans Admin. Hosp., Bronx, N.Y.):* Effect of potassium on electrocardiographic abnormalities produced during insulin shock. Arch. Neurol. & Psychiat. *66*:485-90, October 1951.

Patients in hypoglycemic shock demonstrate electrocardiographic changes, such as a depressed T wave and sagging of the S-T segment. Oral administration of potassium chloride simultaneously with the injection of insulin reverses these electrocardiographic abnormalities and raises the serum potassium level. There is no correlation between serum potassium concentrations and changes in the electrocardiographic pattern. Some theoretical considerations have been offered to explain this discrepancy.

KUETHER, CARL A. *(Dept. of Biochemistry, Univ. of Washington, Seattle):* Tolerance of normal and alloxan-treated rats to intravenous glucose and glucose-1-phosphate. Am. J. Physiol. *167*:355-58, November 1951.

Following intravenous injection of glucose-1-phosphate into normal and alloxan-treated rats, there is a more rapid drop in the blood glucose level than when an equivalent amount of glucose and inorganic phosphate is injected intravenously. The difference between the rates of disappearance of glucose-1-phosphate and of glucose from the blood is greater in alloxan-treated rats than in normal rats. Less of the glucose of intravenous glucose-1-phosphate than of intravenous glucose appears in the urine of normal and alloxan-treated rats. These results suggest that glucose-1-phosphate is more readily utilized than glucose by both the normal and the alloxan-treated rat. These findings support the view that the formation of phosphate esters of glucose constitutes a metabolic block in the utilization of glucose in the diabetic animal.

LAZARUS, SYDNEY S.; VOLK, BRUNO W.; JACOBI, MENDEL; LSADE, WALTER R.; AND ZYMARIS, MICHAEL *(Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N.Y.):* Lymphocytic response of diabetic patients to administration of glucose and insulin. Am. J. Clin. Path. *21*:436-43, May 1951.

In 11 of 22 diabetic patients tested, the intravenous administration of 25 gm. of glucose in a 50 per cent solution was followed by a decrease of the absolute lymphocyte count similar to that found in 12 normal controls. In the other 11 patients, either a moderate increase of the absolute lymphocyte count or a non-significant variation from the fasting count was elicited. The decrease of the absolute lymphocyte count similar to that in the normal person was observed mainly in diabetic patients who gave clinical evidence of pre-existing hepatic or neurogenic disorders but not in patients whose clinical condition was consistent with disturbances of pituitary-adrenal function. It is suggested, therefore, that this method may be a helpful means of distinguishing a pituitary-adrenal diabetes from one based on other factors.

LEVITAN, BENJAMIN A.; AND STEAD, EUGENE, JR. *(Dept. of Med., Duke Univ. Sch. of Med., Durham, N. C.):* Effect in normal man of hyperglycemia and glycosuria on excretion and reabsorption of phosphate. J. Appl. Physiol. *4*:224-26, September 1951.

In nine normal subjects, the tubular reabsorption of phosphate was depressed by 21 per cent when glucose was given intravenously to measure maximal glucose reabsorption (glucose Tm). The mean phosphate excretion increased by 78 per cent, and the clearance of phosphate increased by 100 per cent. The data recorded suggested to the authors that, in addition to breakdown of body protein, the hyperglycemia and glycosuria present in uncontrolled diabetes may also play a part in the loss of phosphate from the body.

LEVITT, LEON M.; AND HANDELSMAN, MILTON B. *(Dept. of Med., State Univ. of N.Y.; State Univ. Med. Center at N.Y.; Coll. of Med.; the Diabetic Clin. of the Long Island Coll. Hosp.; and the Dept. of Med., Univ. Div., Kings County Hosp., Brooklyn):* Orthostatic hypotension in diabetes mellitus: Evaluation of vascular damage on high salt therapy. New York State J. Med. *51*:2249-54, October 1, 1951.

The case history of a patient with orthostatic hypotension which accompanied his diabetic neuropathy is presented in detail. Several dorsal and lumbar sympathetic ganglia examined histologically at necropsy five years later were normal. Treatment with large doses of salt controlled the hypotension; it did not produce hypertension. Following high-salt therapy (25 to 30 gm. daily) over a long period of time (over two and one-half years), an emotional upset was followed by an exacerbation of severe "small vessel" damage in the eyes, heart, and kidneys. The clinical course of this case suggested to the authors that the high salt intake influenced the vascular damage in a manner seen in Selye's adaptation syndrome. However, limited experimental studies with high-salt diets in alloxanized diabetic rats did not bear this out.

LIERE, EDWARD J.; STICKNEY, J. CLIFFORD; AND NORTHUP, DAVID W. *(Dept. of Physiol., Sch. of Med., West Virginia Univ., Morgantown):* Effect of anoxia on intestinal motility and on blood sugar in pups. Am. J. Physiol. *167*:103-07, October 1951.

The effects of anoxic anoxia and of anemic anoxia were studied on the propulsive motility of the small intestine of pups (animals which still had deciduous teeth and were sexually immature). Anoxic anoxia produced a significant decrease in propulsive motility, but anemic anoxia had no significant effect. This is in direct contrast to the findings in adult dogs. The hyperglycemic response of pups to hypoxia was distinctly less than that of adult dogs.

LINDER, G. C.; JACKSON, W. P. U.; AND GRAYCE, I. *(Univ. of Cape Town and Groote Schuur Hosp., Cape Town):* NPH 50 insulin. South African M. J. 25:682-83, September 15, 1951.

NPH insulin was used in 11 diabetics previously treated with globin insulin or a mixture of protamine zinc insulin and plain insulin. Four cases were mild (less than 40 units daily); 5 were intermediate (40 to 80 units); and 2 were severe (60 to 90 units). The patients were almost unanimous in stating that they felt better on NPH, and there was no doubt that many minor and some major hypoglycemic symptoms were obviated.

LIPS, A. C. M. *(Nijmegen, Netherlands):* The excretion of inorganic phosphorus in children after the administration of glucose. Acta med. Scandinav. *141*:1-5, June 11, 1951.

The excretion of inorganic phosphorus after the intake of glucose was studied in children. After the administration of glucose, the phosphate excretion in the urine increases. This phosphate excretion does not always increase parallel with the increase in the diuresis; after the administration of water without glucose, the excretion of inorganic phosphorus increases only slightly or not at all. In adults, unlike children, the inorganic phosphorus in the urine decreases after the injection of glucose.

LUKENS, F. D. W. *(Philadelphia):* Studies on the pathogenesis of diabetes. Canad. M. A. J. 65:334-39, October 1951.

The author presents a general review of the pathogenesis of diabetes on the basis of his own experience and that of others. Growth hormone causes insulin resistance but at the same time leads to an increased secretion of insulin, which prevents glycosuria and facilitates the storage of nitrogen. For optimal protein anabolism, a special equilibrium between these hormones is required. Since the glycosuria and the anti-insulin effects of growth hormone can occur without the pituitary, pancreas, or liver and since the interference with insulin is demonstrable in muscle in vitro, it appears that most of the anti-insulin effect is exerted in the tissues, where growth hormone acts not on the insulin molecule but on the anatomic or chemical site of insulin action.

Experiments are cited which indicate that hyperglycemia stimulates insulin production and is an element to be reckoned with in the pathogenesis of diabetes.

Evidence for the role of alloxan in the production of human diabetes is indicated. Work indicating the presence of oxomalonate in the urine of normal and diabetic subjects is reviewed, and there is a discussion of the evidence that the source of this substance is alloxan.

LUNTZ, G. R. W. N. *(Romsley Hill Sanitorium, Worcs, and Anti-Tuberculosis Center, Birmingham, England):* Insulin loss during injection. Lancet 2:827-28, November 3, 1951.

The author recalls a previous study, in which he showed that, with a 1-ml. syringe and a size 20 needle, the average loss during subcutaneous injection was 22.3 per cent for standard U-80 insulin. Further observations have shown that by using a smaller needle (size 26), the average loss was reduced to 11.9 per cent and with protamine zinc insulin it was only 9.6 per cent. When a 2-ml. syringe and a size 20 needle was used, about 25 per cent of the usual insulin dose was lost because of the volume of fluid left in the dead space of the syringe and the needle. The author recommends the use of a tuberculin-type 1-ml. syringe and a small needle to reduce wastage.

MACKLER, BRUCE; MITHOEFER, JAMES; AND GUEST, GEORGE M. *(Children's Hosp. Res. Foundation, Univ. of Cincinnati):* Glucose utilization in hepatectomized dogs. Proc. Soc. Exper. Biol. & Med. 78:224-26, October 1951.

In four hepatectomized dogs the rate of disappearance of glucose from the blood during the first hour after operation was slower than during the second hour after the intravenous injection of glucose solution. This is in contrast to the findings by Soskin that in completely eviscerated dogs there is no difference in rates of disappearance of blood sugar before and after the administration of glucose. The authors conclude that in hepatectomized animals the intravenous injection of glucose stimulates the secretion of insulin, which accelerates the rate of removal of sugar from the blood by tissues other than liver.

MACNEAL, PERRY S. *(Philadelphia):* The office management of diabetes. Delaware State M. J. *23*:323-38, November 1951.

The author emphasizes the variability of diabetes. He considers it impossible to follow any rigid set of rules, but points out the factors which can contribute to successful treatment.

MALINOWSKI, THEODORE S. *(Dept. of Med., Indiana Univ. Med. Center):* Serum amylase response to pancreatic stimulation as a test of pancreatic disease. Am. J. M. Sc. *222*:440-45, October 1951.

Prostigmine stimulation of the pancreas, with determination of serial serum amylase values for two hours, is of value in cases suspected of chronic recurrent pancreatitis which are seen when clinical symptoms have subsided. A significant elevation of serum amylase values above normal (70 to 240 mg. per 100 cc. in the author's laboratory) is diagnostic. The prostigmine test is a fairly adequate, simple test that has been diagnostic in 81 per cent of 21 cases. The simplicity of the prostigmine test adds to its usefulness. It can be readily performed in any office equipped to do serum amylase determinations.

MANNING, RICHARD PHIL; WHITE, SIDNEY G.; AND CARNE, HERBERT O. *(Van Nuys, Calif.):* Serum lipids in a case of diabetic lipemia retinalis. Am. J. Ophth. *34*:1715-18, December 1951.

Lipemia retinalis is an infrequent complication of hyperlipemia, which is almost always secondary to diabetes mellitus. The condition rarely occurs in nondiabetic hyperlipemia. A case of diabetes mellitus with lipemia retinalis is reported. Fat-filled histiocytes were demonstrated in the bone marrow during the lipemia. These cells disappeared when the blood lipids returned to normal. The lipemia retinalis disappeared without a significant change in the blood fat level and before the disappearance of the fat-filled histiocytes.

MARBLE, ALEXANDER; AND BAILEY, C. CABELL *(George F. Baker Clin., New England Deaconess Hosp., Boston):* Hemochromatosis. Am. J. Med. *11*:590-99, November 1951.

Thirty cases of proved and 17 cases of probable hemochromatosis with diabetes are presented together with postmortem findings in 15 of the proved cases. In the proved cases the diagnosis was verified by skin biopsy, liver biopsy, or autopsy. Three of the 30 proved cases were females. The age at onset of diabetes varied from 36.7 to 78.1 years. Because the onset of symptoms was so indefinite, the date of onset of hemochromatosis could not be established. Three of the 30 patients are living, with duration of diabetes of 13, 8.8, and 5.7 years respectively. Among the fatal cases the average age at death was 57.8 years and the duration of diabetes 4.9 years.

The average insulin requirement was somewhat greater than that of most diabetic patients, and 1 patient died in coma while receiving 1,600 units daily. However, insensitivity to insulin was not invariable; 17 of the 30 cases never took more than 50 units of insulin daily.

The authors believe that with present-day treatment of both diabetes and cirrhosis of the liver a longer life is possible for the patient with hemochromatosis. However, paucity of knowledge regarding the basic defect makes specific therapy impossible as yet. Possible new approaches to this problem are discussed.

MARBLE, ALEXANDER; AND LEECH, RACHEL S. *(New England Deaconess Hosp., Boston):* Total hydrolyzable cystine in the blood serum in diabetes. Bull. New England M. Center *13*:219-21, October 1951.

Total cystine in the blood serum was determined in 52 diabetic and 25 normal individuals. In 76 per cent of the normal persons the total cystine of the serum was between 325 and 375 mg./100 cc., whereas only 15 per cent of the diabetic patients had values within this range and 69 per cent had values below 325 mg./100 cc. The results indicated three tendencies: (1) In the diabetic there was a trend toward a decrease in the total cystine of the serum, with a consequent tendency toward a low cystine-protein ratio. The decrease in total cystine occurred in both fractions of the serum protein but chiefly in the globulin component. (2) There was a definite tendency in the diabetic toward an increased serum globulin with a decreased A/G ratio. (3) In repeated analyses over long periods of time, the individual diabetic tended to have a degree of fluctuation which was greater than that shown by the normal person in serum protein concentration, in total cystine content of protein, and in the cystine-protein ratio.

MARDONES, J.; MONSALVE, M. VIAL; AND PLAZA DE LOS REYES, M. *(Lab. of Exper. Pharmacology and Inst. of Physiological Chemistry, Sch. of Med., Univ. of Chile, Santiago):* Tissue cytochrome C and prevention of experimental atherosclerosis. Science *114*:387, October 12, 1951.

In a feeding experiment upon rabbits on a cholesterol-rich diet, administration of potassium iodide effected an increased cellular content of liver and kidney cytochrome C and inhibited the development of atherosclerosis. Similar results were not obtained in thyroidectomized animals. Since Drabkin has pointed out the positive correlation between thyroid activity and tissue content of cytochrome C, it is suggested that the action of iodide may be the stimulation of thyroid and that the augmentation of cellular cytochrome C must be considered as a factor in the prevention of experimental atherosclerosis by potassium iodide.

MCMAHON, ALPHONSE; ALLEN, HOLLIS N.; WEBER, CLARENCE J.; AND MISSEY, W. C. *(St. Louis):* Hypercholesterolemia. South. M. J. *44*:993-1002, November 1951.

The authors report on 822 unselected cases in general medical practice studied with the purpose of establishing the relationship of total serum cholesterol determined by Bloor's method to age, sex, blood pressure, basal metabolism, and various disease states.

In 554 cases not in disease states known to affect the serum cholesterol content and hence designated as "normal," a progressive increase in cholesterol levels was noted with advancing years, reaching a peak in the decade between fifty and sixty and declining in later decades. The mean value rose from 185 ± 25.6 for the second decade to 252 ± 43.2 for the sixth decade and fell to 192 ± 18.9 in the ninth decade. No significant sex difference was observed.

Deviations from normal cholesterol levels in cases of hypothyroidism, hyperthyroidism, myocardial disease, diabetes, and cholecystitis studied in this series conform to reports in the literature for these diseases. The series of cases classified as having myocardial disease on the basis of abnormal symptoms, history of infarction, ECG, or exercise tolerance presented an age-group curve for serum cholesterol similar in configuration to the "normal" age group curve but running at a level approximately 40 mg. per 100 cc. higher.

MCMILLAN, FOSTER L.; AND SCHEIBE, JOHN R. *(Chicago):* Islet cell tumor of the pancreas. Am. J. Surg. 82:759-61, December 1951.

A twenty-two-year-old woman with a one-year history of afternoon periods of syncope and with demonstrated episodes of severe hypoglycemia was treated by successful removal of a single benign islet-cell tumor. Blood-sugar determinations before and after excision of the pancreatic adenoma were of value in determining the completeness of removal of hyperinsulin-producing tissue.

MILLER, JAMES W. *(Mason Clin., Seattle):* The conservative and prophylactic surgical management of foot lesions in the diabetic. Bull. Mason Clin. 5:63-69, September 1951.

Emphasis is placed on the prevention of frank gangrene by the proper care of superficial infections, bunions, hammertoes, and varicose veins, plus the proper general care of the feet. There is a discussion of how to avoid more drastic procedure by proper selection of patients for amputation of toes and for the transmetatarsal operation.

MIRSKY, I. ARTHUR; FUTTERMAN, PERRY; WACHMAN, JOHN; AND PERISUTTI, GLADYS *(May Inst. for Med. Res., Jewish Hosp., Cincinnati):* The influence of pancreatectomy on the metabolic state of the alloxan-diabetic dog. Endocrinology *49*:73-81, July 1951.

In the dog previously rendered diabetic by alloxan and maintained on a constant dietary intake and insulin dosage, pancreatectomy produces a diminution of the glycosuria and a decrease in the absorption of proteins from the intestinal tract, as revealed by the increase in the percentage of dietary protein lost with the feces. Actually there is an aggravation of the severity of the diabetic state, since the hyperglycemia, glycosuria, and ketonemia observed during a period of fasting and deprivation of exogenous insulin is greater after than before pancreatectomy of the alloxan-diabetic dog. The alloxan-diabetic dog develops a severe ketonemia after phlorhizination and the consequent depletion of hepatic glycogen. The diminished glycosuria following pancreatectomy of the fed alloxan-diabetic dog is attributed to the decreased absorption of carbohydrate precursors, which in turn masks the aggravation of the endogenous metabolic derangement.

MONTAGNA, CARLOS P. (*Buenos Aires*): Present treatment of infantile diabetes. Prensa pediát. 7-8:1, January-April 1951.

A review is made of several phases of treatment, including diet, the use of different types of insulin, and complications. The education of parents and relatives regarding the disease is mentioned as a great factor in its successful treatment. The author considers NPH insulin of great value in the control of infantile diabetes.

MONTAGNA, CARLOS P. *(Buenos Aires):* Treatment of Infantile Diabetes with NPH Insulin. Establecimientos Gráficos Platt, Buenos Aires, 1951.

NPH insulin is as effective in the control of infantile diabetes as the 2:1 mixture, and it prevents the common dosage errors which may occur when the admixture is made. The dose of NPH to be used in transferring patients from the mixture is the sum of the doses of the two insulins in the mixture. In some cases it is advisable to use a light meal at 10 p.m. to prevent nocturnal hypoglycemia.

MOYER, JOHN H.; AND WOMACK, C. RAY *(Dept. of Med., Baylor Univ. Coll. of Med., Houston):* Evaluation of glucose tolerance in seventy-one subjects with glycosuria. Am. J. Med. *11*:247, August 1951. *(Abstract of paper presented at the Fifth Annual Meeting of the Southern Society for Clinical Research, New Orleans, January 27, 1951).*

In an attempt to evaluate variable results obtained when different glucose tolerance tests are used, the one-dose oral (standard), the two-dose oral (Exton-Rose), the postprandial, and the intravenous tests were performed on a heterogeneous group of 71 persons showing glycosuria but no other symptoms of diabetes mellitus. Criteria of normality derived from a similar study. *(Am. J. M. Sc., 219*:161) by the authors on control subjects were used for comparing the tests.

The results showed that the two-dose test is excessively sensitive, that it disagrees with the other tests and yields diabetic results in nondiabetic subjects with significant frequency. The postprandial blood sugar correlates relatively well with the intravenous and standard tests. Because of its simplicity, it is deemed of value as a presumptive test. The intravenous test was found to be less sensitive than the standard, but both are considered satisfactory for clinical diagnostic use. Of the four tests evaluated in this study, the standard oral test is considered to be the most sensitive as well as the most specific. The 24-hour urine glucose excretion did not appear to correlate with the degree of carbohydrate dysmetabolism, probably because of variations in renal threshold.

MUNRO, H. N. *(Dept. of Biochem., The University, Glasgow, Scotland):* Carbohydrate and fat as factors in protein utilization and metabolism. Physiol. Rev. *31*:449-88, October 1951.

The author exhaustively reviews the comparative effects of carbohydrate and of fat upon protein metabolism both from the nutritional viewpoint and from the standpoint of the biochemical mechanisms underlying these metabolic effects.

In the field of nutrition, three aspects of protein-sparing action can be distinguished. First, there is the improvement in nitrogen balance due to increased energy intake, whether the extra intake is derived from carbohydrate, fat, or alcohol. This effect is obtained regardless of whether protein is ingested with or independent of the other foodstuff. Second, there is the enhanced utilization of dietary protein which occurs when carbohydrate is fed together with protein in the diet. This effect is not obtained when fat is substituted isocalorically for carbohydrate; in fact, such substitution leads to a temporary impairment in nitrogen balance. Third, carbohydrate plays a special role in conserving protein of endogenous as well as of dietary origin, for the feeding of carbohydrate to fasting animals reduces nitrogen output, whereas fat feeding generally does not have this effect.

From the metabolic point of view, the above-described effects appear related to the fact that the energy needed for protein synthesis comes from a pool of energy-yielding metabolites to which carbohydrate and fat are the main contributors. The sensitivity of nitrogen balance to a change in either carbohydrate or fat intake suggests that protein metabolism is in dynamic equilibrium with the level of metabolites in this pool. The special protein-sparing action of carbohydrate which is not shared by fat does not appear to depend either on improved synthesis of nonessential amino acids from the carbohydrate or on stimulation of some endocrine gland, but it may result from a short-lived stimulation of protein synthesis due to a temporary increase in the level of available energy shortly after carbohydrate administration.

MURDOCK, THOMAS P. *(Meriden, Conn.):* The modern history of diabetes mellitus—its management. Connecticut M. J. *15*:1064-66, December 1951.

The author discusses the treatment of diabetes and gives his appraisal of NPH insulin. He stresses the frequency of vascular complications.

PALACIOS BERMUDEZ, R.; ITURBE ZABALETA, I.; JIMENEZ CALDERON, F.; AND RODRIGUEZ ARGUELLES, J. *(Mexico City):* Trial with NPH insulin. Rev. Hosp. españ. *1*:7-20, 1951.

Ten moderately severe diabetics were hospitalized and transferred from PZI to NPH insulin, on a standard diet of 1/5 (8:30 a.m.), 2/5 (12:30 p.m.), and 2/5 (6:30 p.m.). Tests for glycosuria and glycemia (venous blood) were performed fasting and 1½ hours after each meal. The results were more favorable with NPH insulin. The division of the same type of diet was subsequently changed to 1/4 (8:30 a.m.), 1/2 (1:30 p.m.), and 1/4 (8:30 p.m.) so as to conform with the division and mealtimes prevalent in Mexico. The same controls described above were repeated. When the glycemic curves are compared, it is found that the most favorable results were attained with NPH insulin and the regimen of "spaced" feedings, i.e., the regimen normally followed in Mexico. The authors conclude that in their study (a) the control was better with NPH than with PZI on a diet of 1/5, 2/5, and 2/5, (b) with a "spaced" diet distribution of 1/4, 1/2, and 1/4, the control was better than with the previous diet distribution; and (c) NPH insulin is perfectly adapted to the diet habits of Mexico.

PANIAGUA, MANUEL E.; AND DOMINGUEZ, ALBERTO *(Presbyterian Hosp., San Juan, Puerto Rico):* The treatment of diabetes mellitus with NPH insulin. Bol. Assoc. méd. Puerto Rico *43*:534-40, October 1951.

An evaluation of the usefulness of NPH insulin in the treatment of diabetes mellitus is presented. Better control with fewer technical difficulites was obtained in 11 of 14 juvenile diabetics; results no better than with other preparations were observed in 1 case of "brittle" diabetes and in 1 patient who would not follow treatment; no follow-up is available in the fourteenth case. Satisfactory control was obtained in 6 of 8 cases of diabetes affecting middle-aged or elderly persons who continued to require insulin (one of them up to 160 units daily); the other 2 were controlled by diet only.

PERRY, SEYMOUR M.; AND ROSENBAUM, SEYMOUR L. *(Coll. of Med. Evangelists, Los Angeles County Hosp., Los Angeles):* Hypopotassemia in untreated diabetic coma. New England J. Med. *245*:847-51, November 29, 1951.

Two patients in diabetic coma are described, with low serum-potassium levels on entry and clinical manifestations of hypokalemia. Early and adequate parenteral potassium administration in the routine treatment of diabetic coma was suggested by the authors.

PETERS, JOHN P. *(Yale Univ. Sch. of Med., New Haven, Conn.):* The interrelationships of foodstuffs in metabolism. Yale J. Biol. & Med. *24*:48-72, September 1951.

Fat is an ideal fuel because its caloric value per unit of mass is so great. If an animal is given a diet devoid of fat but containing enough carbohydrate to supply its caloric needs, it will lose weight and ultimately die with characteristic lesions, including a fatty liver and degeneration of the kidneys. The explanation for this lies in the fact that certain types of fatty acids essential for life cannot be formed in the body.

Formation of fat from carbohydrate is the main pathway for the continuing metabolism of carbohydrate, and obstruction of this pathway will immediately cause glucose to back up in the blood and to pour into the urine. Studies with isotopic labeled compounds have lent strength to those who have held that conversion of carbohydrate to fat is essentially an irreversible reaction.

If a dose of glucose is given to an adult male who has been starved for forty-eight hours, the blood-sugar curve will resemble that of a diabetic and some sugar is likely to appear in the urine. Some time must elapse before normal utilization of carbohydrate is resumed. A similar state of starvation diabetes can be induced more easily in women or children. Appearance of this state can be accelerated by exercise. After a hypoglycemic reaction, if the subject is not immediately given carbohydrate, ketosis will regularly appear. At this time a dose of carbohydrate will provoke excessive and prolonged hyperglycemia, a diabetic type of reaction.

Mention is made of the hormones which regulate combustion of carbohydrate. The growth hormone will produce either a very severe temporary diabetes or a permanent one. When the latter occurs, it can be demonstrated that this is a consequence of the widespread degeneration of the islets of Langerhans. It is believed that in susceptible species such degeneration is due to the marked hyperglycemia that is associated with the administration of growth hormone.

PHILLIPS, D. M. P. *(Courtauld Inst. of Biochemistry, Middlesex Hosp. Med. Sch., London):* Further observations on the action of chymotrypsin on insulin. Biochem. J. 49:506-12, September 1951.

Throughout the digestion of insulin by chymotrypsin, the enzyme remains almost fully active and the digestion rate is unaffected by the presence of urea or the products of the digestion. The *p*H-digestion rate curve for this proteolysis has two optima, at *p*H 8.6 and 9.5. The double optimum is not due to inactivation of part of the insulin or the enzyme, and the bonds split at *p*H 7.6 and 9.9 appear to be the same. Insulin is inactivated at the same rate at *p*H 7.6 and 9.9 by chymotrypsin. The amino groups revealed by the proteolysis belong mostly to amino acids other than tyrosine and phenylalanine and, together with the distribution of tyrosine and phenylalanine among the products, give indirect support to the specificity rule suggested for this enzyme by other workers. The degradation has the character of an "all-or-none" reaction. Every molecule degraded has undergone the fission of 13 or 14 bonds, irrespective of the number of intact insulin molecules present.

RABINOVITZ, M.; STULBERG, M. P.; AND BOYER, P. D. *(Div. of Agr. Biochem., Univ. of Minn., St. Paul):* The control of pyruvate oxidation in a cell-free rat heart preparation by phosphate acceptors. Science *114*:641-43, December 14, 1951.

The authors present data with respect to the oxidation of pyruvate indicating the role of glucose as a phosphate acceptor in the hexokinase transfer of phosphate to glucose as adenosine triphosphate is converted to adenosine diphosphate; the data indicate the compulsory nature of the phosphorylation coupled with the oxidation of pyruvate and the mutual regulations of these two phenomena through the coupled enzymic reactions.

ROBSON, G. B. *(Stanford Univ. Sch. of Med., San Francisco):* Weight reduction in treatment of diabetes mellitus. Stanford M. Bull. 9:260-61, November 1951.

A case is presented of a female patient who went into severe diabetic coma while obese and who had complete remission of the chemical findings of diabetes mellitus after weight reduction of 30 pounds. Five years later, after regaining the lost weight, she returned with the characteristic findings of diabetes mellitus. The author feels that the cardinal error in diabetic management is failure to recognize the extreme importance of weight reduction in the overweight diabetic. In addition, he believes that overweight diabetics who remain heavy commonly have more complications (diabetic retinitis, renal lesions, and so forth), whereas in a group who have lost weight and "cured" their diabetes such complications have not arisen.

ROOT, HOWARD F.; STORY, ROBERT D.; AND CORTESI, JOSEPH B. *(New England Deaconess Hosp., Boston):* Diabetic coma versus diabetic nephropathy: Hazards of factitious insulin resistance, oliguria and hyperkalemia. New England J. Med. *245*:765-70, November 15, 1951.

Uncomplicated diabetic coma occurring at the discovery of diabetes in a child and uremic coma as a late complication of childhood diabetes are described. Factitious insulin resistance may result when glucose is injected at the height of diabetic coma before insulin actually becomes effective. The pathology of diabetic nephropathy in juvenile diabetes of long duration includes Kimmelstiel-Wilson lesions in the glomeruli, chronic pyelonephritis, marked arteriolosclerosis, and generalized arteriosclerosis. Uremic acidosis simulated diabetic coma in the presence of soft eyeballs, dehydration, hyperglycemia, and typical air hunger but was differentiated by the demonstration of the lack of increased ketone bodies in the blood. Fatal hyperkalemia with marked electrocardiographic changes occurred in a patient with uremic acidosis, although no potassium solution had been administered.

ROSE, THOMAS F. *(Dept. of Surgery, and Unit of Clinical Investigation, Royal North Shore Hosp. of Sydney, Sydney):* Pancreatitis at the Royal North Shore Hospital of Sydney from 1925 to 1950. M. J. Australia 2:454-58, October 6, 1951.

A review has been made of 89 cases of pancreatitis at the Royal North Shore Hospital from 1925 to 1950. It has been shown from these cases that the various syndromes of pancreatitis (acute relapsing and chronic) can be correlated and are part and parcel of the one disease entity. The various sequelae are discussed, along with the association of pancreatitis with other diseases, especially diabetes mellitus, gallbladder disease, and hepatitis. With the exception of gallbladder disease, these greatly increase the mortality. The patients were followed up as far as possible, some for twenty-three years, and during this time 31 died.

ROTTENSTEIN, HANS; HORWITZ, ORVILLE; MONTGOMERY, HUGH; SAYEN, ANN; AND SIEMS, LAWRENCE L. *(Peripheral Vascular Section, Edward B. Robinette Foundation, Med. Clin., Hosp. of Univ. of Pennsylvania):* The vasodilator effect of priscoline in patients with ischemic extremities. Am. J. M. Sc. *221*:661-66, June 1951.

The effect of intravenous priscoline on digital cutaneous blood flow, cardiac output, pulse rate, mouth temperature, and respiration was studied in a group of 20 patients with peripheral arterial disease compared with an equivalent number of normal individuals.

The patient's "maximum" blood flow in the periphery was determined by vasodilatation in response to a combination of reflex heat and a meal. "Maximum" flow was correlated with the flow obtained by priscoline. The "basal vascular tone" of each patient was determined.

Priscoline was more effective in increasing digital cutaneous blood flow in patients with arterial disease than in the normal controls. In these patients the digital cutaneous blood flow produced by priscoline was about half of that produced by a combination of food and heat. The increase in flow was, in most instances, still apparent at the termination of the test, 40 to 115 minutes after the administration of the drug. There was no relationship between the effect of priscoline and "basal vascular tone."

There was little change in cardiac output and blood pressure, except in a few drug-sensitive individuals. This, again, suggests a fairly selective action of priscoline as a (digital) cutaneous vasodilator.

SABATIER, J. *(Baton Rouge Clin., Baton Rouge, La.):* Surgery in diabetes. New Orleans M. & S. J. *104*:89-91, September 1951.

Advances made in the study of diabetes, fluid and electrolyte economy, nutrition, antibiotics, and peripheral circulation have made it possible to offer diabetics requiring surgery for incidental, nonrelated conditions a margin of safety comparable to that for nondiabetics. These same advances have made the surgical approach to the diabetic with failing lower-extremity circulation considerably more conservative.

SANCETTA, SALVATORE M.; AYRES, PERRY R.; AND SCOTT, ROY W. *(Cleveland):* The use of vitamin B_{12} in the management of the neurologic manifestations of diabetes mellitus, with notes on the administration of massive doses. Ann. Int. Med. *35*:1028-48, November 1951.

In a series of 12 cases of diabetic neuropathy, treatment with crystalline vitamin B_{12} intramuscularly was given to the exclusion of therapy other than insulin and dietary control. In 3 cases, the authors reported a complete neurologic remission, in 1 a complete remission after a partial relapse, in 3 almost complete remission, in 3 improvement, and in 2 questionable improvement. The variable response appears to be determined by the extent of vascular damage as well as by the reversibility of injury to nerve cells. A satisfactory regulation of the diabetes with insulin and diet is not insurance against the development of neurologic derangements; however, improvement is not to be expected unless such effective regulation is instituted. It is doubtful whether intrinsic spinal-cord lesions can be reversed. Exact dosage of B_{12} has not been established, and the amount and frequency of administration will depend on the factors already mentioned. A flexible dosage of 15 to 30 micrograms daily during the first seven to fourteen days followed by a maintenance dosage of 15 to 30 micrograms once or twice weekly is recommended.

SANGER, F.; AND TUPPY, H. *(Biochem. Lab., Univ. of Cambridge, England):* The amino-acid sequence in the phenylalanyl chain of insulin. 1. The identification of lower peptides from partial hydrolysates. Biochem. J. *49*:463-81, September 1951.

The authors fractionated partial hydrolysates of fraction B (Sanger, F.: Biochem. J. *44*:126, 1950) of oxidized insulin by paper chromatography and determined the structure of the resulting peptides. They concluded that the following amino-acid sequences are present in this fraction: phenylalanine, valine, aspartic acid, glutamic acid, histidine, leucine, cysteic acid, glycine, threonine, proline, lysine, alanine, glycine, glutamic acid, arginine, glycine, tyrosine, leucine, valine, cysteic acid, glycine and serine, histidine, leucine, valine, glutamic acid, alanine.

SANGER, F.; AND TUPPY, H. *(Biochem. Lab., Univ. of Cambridge, England):* The amino-acid sequence in the phenylalanyl chain of insulin. 2. The investigation of of peptides from enzymic hydrolysates. Biochem. J. *49*:481-90, September 1951.

The authors subjected fraction B of oxidized insulin to hydrolysis by pepsin, trypsin, and chymotrypsin. The resulting peptides were fractionated by paper chroma-

tography, and their structure was investigated. It was concluded that the structure of the phenylalanyl chains of insulin is phenylalanine, valine, aspartic acid (NH_2), glutamic acid (NH_2), histidine, leucine, cysteic acid, glycine, serine, histidine, leucine, valine, glutamic acid, leucine, tyrosine, leucine, valine, cysteic acid, glycine, glutamic acid, arginine, glycine, phenylalanine, phenylalanine, tyrosine, threonine, proline, lysine, alanine.

SCHWAB, HENRY *(Goldwater Mem. Hosp. and the Metabolic Div., St. Clare's Hosp., New York City):* New concepts on "brittle" diabetes. New York State J. Med. *51*:2647-49, November 15, 1951.

In discussing "brittle" diabetes, the author dwells on the large and irregular waves of hyperglycemia and hypoglycemia which come on unexpectedly, without any change in diet, insulin dose, or interference by physical activity. He reviews some recent clinical and experimental data pertaining to the blood-sugar level and insulin secretion and discusses their theoretic and practical implications in "brittle" diabetes.

SCOTT, G. I. *(Royal Infirmary, Edinburgh, Scotland):* Discussion on diabetic retinopathy. Proc. Roy. Soc. Med. *44*:742-47, August 1951.

During the past few years the author, in conjunction with Dr. Halliday Croom, has examined 150 diabetics, all of whom have had the disease for periods varying from fifteen to twenty-six years. A preliminary report on the first 60 cases was published in 1949. A careful analysis of the case records was made in an attempt to assess the relationship between the severity or control of the diabetic state and the development of degenerative changes. The severity of the diabetes was assessed by the dosage of insulin required, and the control of the condition by the general well-being of the patient, the degree of glycosuria, and the frequency of reactions. In this series, as in a previous review, there was no significant correlation between the severity of the diabetes and the development of cardiovascular or retinal complications. In regard to the control of the diabetes, it was reported in the review of the first 60 cases that no evidence of any correlation between the occurrence of vascular or retinal changes and the control of the diabetic state was found. A study of the present larger series of 150 patients seems to suggest, however, that control of the diabetic state may, in fact, be an important factor in lessening the incidence or degenerative changes.

SCOW, ROBERT O.; AND FOGLIA, VIRGILIO G. *(Nat. Inst. of Arthritis and Metabolic Diseases, Nat. Inst. of Health, U.S.P.H.S., Federal Security Agency, Bethesda, Md., and Inst. de Biol. y Med. Exper., Buenos Aires):* Effect of neonatal thyroidectomy, age and sex on intestinal absorption and tolerance of orally administered glucose. Am. J. Physiol. *166*:541-49, September 1951.

Oral glucose tolerance was decreased in rats thyroidectomized at birth when compared with normal rats of similar size or age. Thyroidectomized rats absorbed glucose per unit of body size more slowly than normals of like size but equally as fast as normals of the same age. Motility of the gastrointestinal tract was normal in the absence of the thyroid. These tests in thyroidectomized rats, with one possible exception, were not affected by minute amounts of thyroid remnants which were capable of stimulating body weight gain and, to a lesser degree, development of gonads and skeleton. The total amount of glucose absorbed by normal rats increased with size and age until the body weight exceeded 180 gm., after which there was no change. There was an inverse relation with body size when the intestinal absorption rate was expressed as the amount absorbed per 100 gm. of body weight. The higher and shorter glucose tolerance curve observed in young animals could be related to a faster absorption rate. There was no effect of sex on intestinal absorption of glucose in normal rats when animals of similar size were compared. Similarly the sex difference in the oral glucose tolerance test, observed only in 115-day-old rats, was related to size difference. It is suggested that the effects of age and sex on oral glucose tolerance, intestinal absorption, and gastrointestinal motility in normal rats were secondary to their effect on body size.

SEGALOFF, ALBERT; AND MANY, ANNE S. *(Dept. of Med., Tulane Univ., and Endocrine Res. Labs. of Alton Ochsner Med. Foundation, New Orleans):* The role of adrenal steroids and ACTH in gluconeogenesis: A study in phloridzinized animals. Endocrinology *49*:390-400, September 1951.

Adrenalectomy leads to a large decrease in the glucose and nitrogen excretion and to complete suppression of ketone excretion in fasting phlorizinized rats. Excretion of glucose and nitrogen can be elevated by administra-

tion of various 11-oxygenated steroids and desoxycorticosterone acetate. With several compounds, it is possible to raise the ketone excretion above that of the intact controls. ACTH in large doses leads to an increase in urinary glucose unaccompanied by an increase in nitrogen but accompanied by a substanial increase in ketones.

SEIFTER, SAM *(State Univ. of New York, Brooklyn):* The effects of dietary deprivation of potassium on heart glycogen and on blood glycolysis. J. Lab. & Clin. Med. *38*:78-83, July 1951.

Rats deprived of dietary potassium for periods of time varying from seven to seventy-seven days show a comparatively rapid absolute increase in the glycogen contents of their hearts as compared with suitable controls. The cardiac glycogen level of such potassium-starved rats, which is of the order of twice the normal value, can rapidly be restored to the control level by realimentation with potassium for several days. Rats maintained on a potassium-deficient diet for forty-nine and seventy-seven days respectively exhibited no abnormal blood glucose and lactic acid levels and no over-all qualitative or quantitative differences in blood glycolysis.

SHARKEY, THOMAS P. *(Dayton, Ohio):* The national diabetes detection drive—November 11-17, 1951. Ohio State M. J. *47*:1022-26, November 1951.

The author reviews the role of the American Diabetes Association in the organization of the nationwide Diabetes Detection Drive and details the steps necessary for the formation of such a program in a local community. The results of the survey in Dayton, Ohio, in the years 1947-1950 are briefly described. In a group of 212,191 individuals tested, 1,242 new diabetics were found. Glycosuria was found in 1,876 (4.8 per cent) of the 38,528 school children tested postprandially. Among the 1,022 children who had subsequent blood-sugar determinations, 18 new cases of diabetes were discovered.

SIENKNECHT, E. CHARLES *(Acuff Clin., Knoxville, Tenn.):* How strictly should the diabetic be regulated? Acuff Clin. Bull. *2*:14-16, July 1951.

The majority of physicans prescribe an optimal diet and then, by judicious use of insulin, attempt to maintain a normal blood-sugar level and freedom from glycosuria. If diabetes can be improved, it will be possible by this plan. Exceptions to the best management of the diabetic patient should be made from necessity and not because of physician indifference.

SMITH, JACKSON A.; AND BROWN, WARREN T. *(Depts. of Psychiatry and Med., Baylor Univ., Coll. of Med., Houston, Texas):* Psychiatric effects of diabetes occurring late in life. Dis. Nerv. System *12*:278-80, September 1951.

Twenty-five diabetic patients were interviewed in an attempt to evaluate their psychological response to diabetes occurring after maturity. No consistent pattern of behavior was noted prior to the time the disease was discovered. Furthermore the presence of diabetes caused no appreciable change in their behavior whether or not they had been neurotic previously.

SOPHIAN, JOHN *(London, W. 1):* Plasma pentose in pre-eclampsia. Brit. M. J. 2:797, September 29, 1951.

The author debates the theories of causation of eclampsia and pre-eclampsia and concludes that the plasma pentose level may serve as a prognostic and therapeutic guide in pre-eclampsia because of the relationship that is said to exist between this level and overstretching of the uterus, which in turn may give rise to uterorenal reflexes.

SOSKIN, SAMUEL *(Univ. of Chicago Sch. of Med.):* Use and abuse of the dextrose tolerance test. Postgrad. Med. *10*:108-16, August 1951.

Emphasis is placed upon the role of the liver in the pattern of the glucose tolerance test. The oral dextrose tolerance test as ordinarily used and interpreted has limited value. The intravenous glucose tolerance test is favored. The characteristics of intravenous glucose tolerance curves in cases of uncomplicated diabetes and of hepatic disease are described.

SPRING, MAXWELL; AND KAHN, SIDNEY *(The Bronx Hosp., New York City):* Nonclostridial gas infection in

the diabetic: Review of the literature and report of three cases. A.M.A. Arch. Int. Med. *88:*373-77, September 1951.

The presence of gas in infected tissue, especially in a case of diabetes, does not necessarily mean anaerobic clostridial gas gangrene, with its concomitant poor prognosis. It can be due to other gas-producing organisms, such as *Escherichia coli* and there is a good prognosis with conservative surgical and antibiotic therapy.

STAUB, ALFRED; AND VESTLING, CARL S. *(Div. of Biochemistry, Noyes Lab. of Chemistry, Univ. of Illinois, Urbana):* Studies on fructose-1-phosphate with rat liver fructokinase. J. Biol. Chem. *191:*395-99, July 1951.

The authors were able to obtain a stable rat-liver fructokinase preparation. An estimated six to tenfold purification of rat liver fructokinase was accomplished, along with the removal of certain other liver enzymes. The partially purified fructokinase phosphorylates fructose in the presence of added ATP, Mg^{++}, and inorganic phosphate and is devoid of glucokinase activity. Crude barium fructose-1-phosphate (about 70 per cent pure) was isolated as the principal phosphorylation product of fructose by partially purified rat-liver fructokinase.

STEINBRACKER, ARTHUR; BERKOWITZ, SIDNEY; CARP, SOLOMON; EHRLICH, MORTIMER; ELKIND, MORTIMER; SILVER, MURRAY; AND SPITZER, NORMAN *(New York City):* ACTH and cortisone as therapeutic agents in arthritis and some locomotor disorders. Bull. New York Acad. Med. 27:560-76, September 1951.

Glycosuria occurred in 18 of 128 patients treated with ACTH and cortisone. It was transient in 16 and remained in only 2 instances when the drugs were discontinued. It would seem that the 2 instances of persistent glycosuria represented latent diabetes activated by treatment.

STEPANTSCHITZ, G.; AND KRESBACH, E. *(Med. Clin. Univ. of Graz, Austria)*: Observations on the behavior of blood sugar in rheumatic patients following the administration of insulin. Klin. Wchnschr. 29:549-50, August 15, 1951.

Following fasting blood-sugar determinations, 10 units of Insulin-Novo were injected subcutaneously into a series of sixteen patients with clinically manifested rheumatic disease, and blood-sugar determinations were made 15, 30, 45, 75, 105, and 135 minutes later. In healthy control subjects, a fall in blood sugar was noted as early as fifteen minutes following the injection; it reached its maximum in forty-five minutes, and there was a subsequent gradual rise. In contrast to these normal curves, a rise in blood-sugar values was recorded in nine of the sixteen untreated chronic rheumatic patients as early as fifteen minutes following the injection (5 to 35 mg. per cent), and a gradual fall was not seen until some time had elapsed. This paradoxical rise in blood sugar could not be attributed to a possible hyperglycemic factor which might have been present in the insulin preparation used, since in the authors' estimation Insulin-Novo is the only insulin preparation definitely free of such factor. The assumption that insulin, through an intermediary action of the hypophysis, provokes an increased production and secretion of cortisone in some rheumatic patients might explain the paradoxical rise in blood sugar following the injection of insulin.

STEPHEN, JOAN M. L. *(Courtauld Inst. of Biochemistry, Middlesex Hosp. Med. Sch., London):* Degradative studies on the "core" resulting from chymotryptic digestion of insulin. Biochem. J. 49:629-35, October 1951.

The dinitrophenyl derivative of the "core" of the insulin molecule resulting from chymotryptic digestion of insulin has been oxidized with performic acid, and three fractions, which differ in solubility, have been isolated. The core itself has been oxidized, and the main product after treatment with fluorodinitrobenzene or benzoyl chloride has in each case been separated into four fractions. These benzoyl or dinitrophenyl fractions have been analyzed for sulfur. The dinitrophenyl fractions with the exception of one are complex, having a variety of N-terminal amino-acid residues. One dinitrophenyl fraction, about 13 per cent of the total product, has a glycyl end group, a molecular weight of about 2,000, and a high cysteic acid content. A terminal peptide, yielding on acid hydrolysis N-dinitrophenylglycine, isoleucine, valine, glutamic acid, and leucine, has been split from it by Pancreatin.

STEPHENS, JOHN W.; DONALDSON, ROBERT M., JR.; AND MARBLE, ALEXANDER *(George F. Baker Clin., New Eng. Deaconess Hosp., Boston):* Use of mixtures of NPH and unmodified insulins. A.M.A. Arch. Int. Med. *88:*356-61, September 1951.

Data obtained through the study of 23 boys in the

Elliott P. Joslin Camp for Diabetic Boys suggest that the giving of a mixture of crystalline (or regular) insulin with NPH insulin produces an effect comparable with that obtained when the two insulins are given separately. This is probably due to the fact that the NPH insulin, containing a smaller amount of protamine, does not allow the degree of absorption noted when crystalline insulin is mixed with protamine zinc insulin. Since the mixture of NPH and crystalline insulins in a syringe gives essentially the same results as the injection of the two insulins separately, the simultaneous use of crystalline and NPH insulin in the control of certain cases becomes more practicable. Such cases are, of course, those in which the use of NPH insulin alone allows significant hyperglycemia after breakfast.

STETTEN, DEWITT, JR.; WELT, ISAAC D.; INGLE, DWIGHT, J.; AND MORLEY, ERVING H. *(Div. of Nutrition and Physiol., The Public Health Res. Inst. of the City of New York, Inc.; and Res. Lab., The Upjohn Company, Kalamazoo, Mich.):* Rates of glucose production and oxidation in normal and diabetic rats. J. Biol. Chem. *192*:817-30, October 1951.

By means of continuous intravenous injection of a solution of C^{14} glucose into anesthetized rats, constant levels of specific activity of urinary, and presumably circulating, glucose were attained in untreated, phlorizinized, and alloxan-diabetic rats. From the specific activities of injected and excreted glucose and the rate of injection, the rate of formation of glucose from sources not derived from the infused glucose has been calculated. This rate, found to be 14 to 15 mg. per 100 gm. of rat per hour in the normal and in the phlorizinized animals, exhibited a statistically barely significant increase to about 21 mg. per 100 gm. of of rat per hour in the alloxan-diabetic rats. From the specific activity of the exhaled CO_2, a pronounced decrease in rate of total oxidation of glucose was observed incident to phlorizin or alloxan administration. The normal rat was estimated to oxidize 11.5 mg. of glucose per 100 gm. of rat per hour, whereas the phlorizinized and alloxan-diabetic rats oxidized 2.6 and 4.5 mg. per 100 gm. per hour respectively.

STETTEN, MARJORIE R.; AND STETTEN, DEWITT, JR. *(Div. of Nutrition and Physiol., Public Health Res. Inst. of the City of New York, Inc.):* Metabolism of sorbitol and glucose compared in normal and alloxan-diabetic rats. J. Biol. Chem. *193*:157-65, November 1951.

The authors compared the metabolic fates of glucose and sorbitol following intraperitoneal injection of these substances uniformly labeled with C^{14} into well-nourished normal and alloxan-diabetic rats. Sorbitol carbon was abundantly recovered in carbon dioxide, urinary glucose, liver and muscle glycogen, and other tissue constituents. In normal rats, sorbitol was oxidized to carbon dioxide at least as extensively as was glucose, but sorbitol was somewhat less effective as a precursor of muscle and liver glycogen than was glucose.

In the diabetic rat, sorbitol was strongly glycogenic, and following injection of either glucose or sorbitol, the major portion of the carbon administered was excreted in the urine. The extent of oxidation of both test substances to carbon dioxide was markedly diminished in the presence of diabetes.

STOWERS, J. M.: *Med. Unit, Univ. Coll. Hosp. Med. Sch., London*): Hyperfunction of the adrenal cortex and insulin resistance in diabetic ketosis. Clin. Sc. *10*:487-96, November 1951.

Studies of the urinary output of reducing, water-soluble ketonic steroids (the fraction which contains adrenal glucocorticoids) have been made in eleven cases of diabetic ketosis. The output of these steroids was four to twenty-three times as high in ketosis as in these same patients in their basal state. When serial determinations of reducing steroid excretion were made during recovery from ketosis, a relationship was noted between this index of adrenocortical overactivity and the insulin resistance, as measured by the ratio of the total carbohydrate calories to the insulin dose. ACTH was given to two such cases when they had fully recovered. Similar increases in reducing steroid excretion followed, and there was a coincident marked increase in insulin requirement. A male patient in diabetic ketosis was given testosterone propionate for eleven days as well as the usual treatment for the ketosis. The initially high reducing steroid excretion decreased unusually rapidly, more rapidly than the insulin requirement. It is suggested that the testosterone may have depressed endogenous ACTH production and that at least some of the decreased insulin resistance was unassociated with adrenocortical overactivity. Well-balanced, normally insulin-sensitive diabetics have reducing steroid outputs within the normal range, and balanced, insulin-resistant diabetics do not have reducing steroid excretions increased in proportion to the resistance. It is

concluded that the adrenal cortex may mediate a large part, but not all, of the increased insulin resistance accompanying diabetic ketosis.

STRISOWER, E. H.; CHAIKOFF, I. L.; AND WEINMAN, E. D. *(Div. of Physiol. of the Univ. of California Sch. of Med., Berkeley)*: Conversion of C^{14}-palmitic acid to glucose. J. Biol. Chem. *192*:453-63, October 1951.

The possibility that naturally occurring, long-chain fatty acids can be incorporated into glucose was studied in normal and in alloxan-diabetic rats with the aid of palmitic acid labeled with C^{14}. It was found that the labeled carbons of palmitic acid -1-C^{14} and palmitic acid -6-C^{14} are incorporated into glucose in both normal and diabetic rats. From the results obtained, the authors estimated that the contribution of fatty acids to glucose is less than 5 and 10 per cent of the total glucose turned over per hour in normal and diabetic rats respectively. These values represent the lower limit of glucose synthesis from fat. The authors suggest that the actual importance of this process may be far greater than these minimal values would lead one to believe.

SUGAR, SAMUEL F. N.; AND ALPERT, LOUIS K. *(Washington, D. C.)*: Clinical comparison of intermediate insulins in the control of severe diabetes. Am. J. Med. *11*:516, October 1951 *(Abstr. of paper presented at the Eastern Sectional Meeting in Washington, D. C., of the American Federation for Clinical Research, December 9, 1950)*.

Eight patients with severe diabetes, requiring 30 or more units of insulin a day, were given equivalent doses of three types of insulin: globin zinc insulin, 2:1 mixtures of regular and protamine zinc insulin, and NPH 50. Each type of insulin was used for periods of four to seven days. Diet and physical activity were maintained at a constant value. Blood sugars were determined before meals at 8 a.m., at noon, and at 4 p.m. Fasting blood-sugar levels of 150 mg. per cent or less occurred about one and one-half times more often with globin insulin and 2:1 mixtures than with NPH 50. At noon, blood-sugar values below 200 mg. per cent were observed with equal frequency with all three types of insulin. At 4 p.m. the intensity of action was approximately equal with all the types of insulin used. Hypoglycemic reactions occurred only on two occasions, both times with 2:1 mixtures.

On the basis of these findings, the authors conclude that the most satisfactory control, without hypoglycemic reactions, was obtained with the use of globin zinc insulin. NPH 50 insulin gave good control, but fasting blood-sugar values below 150 mg. per cent were obtained only two-thirds as often as with the other two. Although the 2:1 mixtures were considered to give the best control on the basis of the blood-sugar levels, the authors would place this type of insulin in a less desirable position in relation to the other two because of the occurrence of hypoglycemia in two instances.

SVEC, MURIEL; JOHN, H. IVY; AND FREEMAN, SMITH *(Dept. of Exper. Med., Northwestern Univ. Med. Sch., Chicago)*: Free plasma levels and urinary excretion of eighteen amino acids in normal and diabetic dogs. Am. J. Physiol. *167*:182-91, October 1951.

Data have been compiled on the total urinary and plasma-free amino acids of dogs rendered diabetic through pancreatectomy or administration of alloxan. These values were compared with those obtained on the same animals prior to production of the diabetic state. Four behavior patterns were exhibited among the plasma amino acids. Only leucine, isoleucine, and valine exhibited fasting plasma levels that were significantly above their normal range. During uncontrolled diabetes, the 24-hour total urinary excretion of fifteen out of eighteen amino acids was significantly elevated. Only tryptophane, methionine, and cystine were not increased significantly in the urine during periods of uncontrolled alloxan and pancreatectomy diabetes. Evidence is presented which suggests that an increased formation of glycine and some other amino acids may occur during uncontrolled diabetes.

SWANK, ROY L.; AND WILMOT, VALERIE *(Dept. of Neurology and Neuro-Surgery, McGill Univ., and Montreal Neurological Inst., Montreal)*: Chylomicra: Their composition and their fate after intravenous injection of small amounts of heparin. Am. J. Physiol. *167*:403-12, November 1951.

The authors determined the lipid composition of the chylomicra by differential analysis of the whole plasma and of its cleared subnatant portion after high-speed centrifugation. The determinations indicate that the lipid content of the chylomicra is approximately 97 per cent of neutral fat and 3 per cent of free cholesterol.

During lipemia, approximately one-third of the total plasma neutral fat and three-fourths of its increase over fasting levels may be contained in the chylomicra.

Intravenous injections of heparin into dogs with lipemic plasmas result in marked clearing of the plasmas. In four experiments, lipid analyses showed that this clearing was accompanied by a shift of neutral fat from a visible state (chylomicra) to an invisible or dissolved state in the plasma. In one experiment the clearing of the plasma was accompanied by a sharp drop in the amount of visible neutral fat (chylomicra) without significant change in the invisible or dissolved neutral fat. Lesser changes in other lipid fractions, some of questionable significance, were also observed.

SWEENEY, J. SHIRLEY *(Gainesville, Texas):* The South's first full summer camp for diabetic children and observations on use of NPH insulin. South. M. J. *44:*1157-60, December 1951.

The author reports on the initiation and operation of a full-time diabetic camp in Gainesville, Texas, which cared for 70 children during two six-week semesters. It is concluded that NPH insulin is as good as, and probably superior to, other forms for children participating in summer camp life. Three children were entirely withdrawn from insulin.

SWIFT, H. B. N.; SETHI, MOHAN SINGH; AND SINGH, AMAR *(Med. Coll., Amritsar, India):* Studies on the hypoglycemic effect of *Tephrosia purpurea* var. *pumila:* II. Effect of rutin on blood-sugar levels of rabbits. Indian M. Gaz. *86:*42-45, February 1951.

The effect of rutin on the blood sugar concentration of normal rabbits and rabbits rendered diabetic by injection of alloxan has been determined. Rutin raises the blood sugar level of normal rabbits. It has no demonstrable effect on blood sugar levels of rabbits rendered diabetic by the intravenous injection of alloxan.

SZEPSENWOL, J.; AND MICHALSKI, J. V. *(Dept. of Anatomy, Emory Univ. Schs. of Med. and Dentistry, Emory Univ., Ga.):* Glycogenolysis in the liver and glycogen body of the chicken after death. Am. J. Physiol. *165:*624-27, June 1951.

In the chicken, unlike the mammal, the breakdown of glycogen is limited. In the glycogen body there seems to be no breakdown during starvation or after death. In the liver the glycogen diminishes greatly during starvation and only to a slight extent after death.

TERRIERE, L. C.; AND BUTTS, JOSEPH S. *(Dept. of Chemistry, Oregon State Coll., Corvallis):* The influence of amino acids on glycogen formation studied with deuterium. J. Biol. Chem. *190:*1-5, May 1951.

The authors studied the effect of amino acids on glycogen formation when fed with glucose by the technic of enriching the body water of a rat with D_2O and following the rate of incorporation of this isotope into glycogen as used by Stetten and Boxer. Thus, the effect of amino acids would be superimposed upon that of glucose and the deuterium uptake by the newly formed glycogen would change accordingly. A study was made of the deuterium uptake in the glycogen formed by rats fasted for 48 hours and then fed glucose or glucose-amino acid mixtures. Glycine, DL-alanine, DL-isoleucine, and DL-leucine were the amino acids used. Feeding glucose to rats with a body water level of 1.3 per cent deuterium oxide gave an exchange ratio of 30.7 with experiments extending 3 to 24 hours. When DL-alanine, glycine, or DL-isoleucine was fed along with the glucose, a significantly increased exchange ratio occurred. Under similar conditions, DL-leucine failed to affect the exchange ratio.

The authors state that their studies support the concept of the metabolic pool. This theory implies that after initial modifications in the first stages of metabolism, the foodstuffs become incorporated into a system of common carbon fragments no long distinguishable as to origin. Since water is undoubtedly a constituent of this pool, heavy water can be used to label the fragments. Thus, when glucose is absorbed into a medium containing D_2O, the fact that deuterium is found in the glycogen subsequently synthesized indicates that fragments have been thrown into the metabolic pool in sufficient amounts to meet body needs and to allow the building up of an end product. When alanine, glycine, or isoleucine was fed, the exchange ratio was increased, indicating that a greater uptake of deuterium was occurring and that the equilibrium was being shifted to utilize different fragments. This view is strengthened when the results after feeding leucine are considered. This amino acid apparently does not cause glycogen synthesis, and therefore should not cause an increase in the exchange ratio. The exchange ratio of 33 was found when leucine was fed with glucose, and

this is very nearly the value given when glucose alone was fed. The authors contend that with this technic, one is able to determine the glycogenic effects of compounds that, when fed alone, cause only slight glycogen formation.

TEST, C. T.; RICKETTS, H. T.; STEINER, P. E.; PETERSON, E. S.; LINTS, H. A.; AND TUPIKOVA, N. *(Univ. of Chicago Sch. of Med. Chicago):* Some effects of alloxan on the canine kidney, with special reference to the glomerulus. Proc. Soc. Exper. Biol. & Med. *78*:21-24, October 1951.

In two dogs which did not become diabetic following repeated doses of alloxan, serial biopsies of the kidney showed the late development of glomerular lesions. These lagged behind the usual tubular degeneration and appeared both in time and in type to be subsequent to the latter. Similar studies on dogs receiving a single dose of alloxan and surviving for comparable periods of time showed only minimal glomerular changes.

TEXTER, E. CLINTON, JR.; REDISCH, WALTER; AND STEELE, J. MURRAY *(N. Y. Univ. Res. and Med. Serv., Goldwater Mem. Hosp., Welfare Island, New York City):* Induced intermittent claudication. Am. J. M. Sc. *222*:653-57, December 1951.

The induction of intermittent claudication with the friction-belt bicycle ergometer is described.

Good correlation was found between clinical evidence of arterial insufficiency in the legs and induced claudication.

The exercise tolerance test is no better than a good history and clinical examination in the diagnosis of obliterating peripheral arteriosclerosis. All patients in whom claudication could be produced had a previous history of intermittent claudication.

THONE, H.: Heredity of diabetes mellitus: Question of advisability of marriage of diabetic patients. Med. Klin. *46*:327, March 16, 1951 [*Abstr. from* J.A.M.A. *146*:-1081, July 14, 1951].

A predisposition to diabetes is hereditary, but the transmission is more often recessive than dominant. Although the likelihood of developing the disease is much greater for a child with a familial predisposition to diabetes than for one without such predisposition, the author does not believe that a diabetic person should be forbidden to marry. If both partners have a family history of diabetes, then the likelihood of diabetes in the offspring is great.

THORLEY, A. S.; AND KAY, W. W. *(Belmont Hosp., Sutton, and Mental Hosp. Group Lab., West Park Hosp., Epsom, England):* Some biochemical aspects of hypoglycemic coma (I). Proc. Roy. Soc. Med. *44*:969-73, November 1951.

Half-hourly observations are reported on the changes in blood glucose, serum inorganic phosphates, potassium, protein, sodium, chloride, and bicarbonate in men undergoing insulin shock therapy. The most uniform changes occurred in blood glucose, serum inorganic phosphate, and potassium. The phosphate and potassium changes agreed with those usually found when glucose is removed from the blood. Of particular interest was the unsustained attempt at restoration of blood glucose in stupor, when the transient rise in the blood glucose curve was associated with a marked fall in phosphate and especially potassium, which is thought to be related to the influx of glucose into the blood. The outstanding features of deep hypoglycemia were the uniformly low blood sugar and consistently low bicarbonate readings. The latter have been linked with failure to utilize oxygen.

TIPSON, R. STUART; AND CRETCHER, LEONARD H. *(Dept. of Research in Organic Chemistry, Mellon Inst., Pittsburgh):* Reduction of alloxan in aqueous solution: Effect of certain organic reductants at *p*H 1.6. J. Am. Pharm. A. (Scient. Ed.) *40*:440-46, September 1951.

l-cysteine, glutathione, and L-ascorbic acid have no reducing effect on alloxan in aqueous solution at *p*H 1.6. At *p*H 1.6, there is no evidence of combination of alloxan with glutathione to give a substance whose ultraviolet absorption spectrum exhibited a peak at 305 μ. At *p*H 1.6, *l*-cysteine affords no appreciable protective action against aerial oxidation of alloxantin solution; hence, at this *p*H, dialuric acid is a stronger reducing agent than *l*-cysteine. It is, however, a weaker reductant than hydrogen sulfide.

TSENG, H. C.; WU, W. J.; AND WU, C. K.: Acute pancreatitis. Chinese M. J., *69*:107, 1951 [*Abstr. from* Surg., Gynec. & Obst.; Internat. Abstr. Surg. *93*:460-62, November 1951].

There is no characteristic clinical picture of acute pancreatitis, nor are there pathognomonic physical findings. Many tests have been proposed to aid in the diagnosis. Serum amylase is the most accurate single test and should be carried out in all cases of severe abdominal pain. Other aids in diagnosis are leukocytosis, hyperglycemia, and decrease of the serum calcium. The urine diastase test remains a simple, fairly accurate method while the urine amylase test is not as accurate. Occasionally, glycosuria is also present. Recurrent attacks are not infrequent, and certainly a thorough examination of the biliary and gastrointestinal tracts should be made when the patient has recovered from the acute attack. Diabetes is also a factor following acute pancreatitis and must be watched for.

UDENFRIEND, S.; AND VELICK, S. F. (*Washington Univ. Sch. of Med., St. Louis*): The isotope derivative method of protein amino and end-group analysis. J. Biol. Chem. *190*:733-40, June 1951.

Making use of labeled *p*-iodophenylsulfonyl chloride to cover the end groups of proteins, these authors conclude that bovine insulin contains one glycine and one phenylalanine end group per subunit of 12,000. These results contrast with Sanger's finding of two of each of these amino acids per subunit of 12,000.

UZAN, M.; AND DZIRI, A.: On the variations of glycolytic activity of muscular extracts from animals treated with alloxan. Presse méd. *59*:856, June 16, 1951.

The authors found a constant modification of this activity in mice and *Meriones* (a Moroccan rodent); it was increased during light intoxication and inhibited during the severe period of the disease.

VIETH, G. *(Hamburg):* Diabetes mellitus associated with tuberculosis. Beitr. Klin. Tuberk. *104*:436-49, 1951 [*Abstr. from* Excerpta Med. (Int. Med.) *5*:1116, August 1951].

A report is given on 85 cases (42 men and 43 women), with an average age of 33.5 years, in which diabetes mellitus was associated with tuberculosis. In another group of 600 diabetics, 3.5 per cent were affected with active and 2.5 per cent with inactive tuberculosis in which extrapulmonary localizations were rarely seen to occur. Exudative processes were present in 37.7 per cent, bilateral in 51.8 per cent, and cavernous in 19.4 per cent. The severity of the diabetes does not affect the form of the tuberculosis.

VOGT, M. (*Univ. of Edinburgh*): The role of hypoglycemia and of adrenaline in the response of the adrenal cortex to insulin. J. Physiol. *114*:222-23, June 29, 1951.

Adrenal denervation in rats abolishes neither the ascorbic acid depletion nor the loss of sudanophilic material caused by insulin in the adrenal cortex. In the denervated adrenal the ascorbic acid depletion by insulin was less when the hypoglycemia had been partially checked by injection of glucose. Rats with demedullated adrenals likewise respond to insulin by exhibiting adrenal ascorbic acid depletion. This can be reduced but not abolished by glucose.

VOLK, BRUNO W.; AND LAZARUS, SYDNEY S. *(Brooklyn N. Y.):* A clinical study of the pathogenesis of the diabetic syndrome: Use of a modified glucose insulin tolerance test combined with the change of serum inorganic phosphorus after glucose administration. Am. J. Digest. Dis. *18*:269-74, September 1951.

A modification of Himsworth's glucose-insulin tolerance test is introduced which consists in the administration of 0.1 unit of crystalline insulin intravenously 30 minutes after the intravenous injection of 25 gm. of glucose in 50 per cent solution. This procedure elicited a consistent pattern of response in the 25 normal individuals, the blood sugar falling to fasting level within 45 minutes after the insulin administration. It is hoped that this test, in combination with the determination of the serum inorganic phosphorus decline after glucose administration, may provide assistance in distinguishing three pathogenic factors of the diabetic syndrome: hepatic dysfunction, overactivity of insulin antagonists, and, by exclusion, primary insulin deficiency. It is suggested that such differentiation may be of practical value for the treatment of the diabetic syndrome.

WAJZER, JACQUES; AND ZELNIK, RAYMOND: Transformation of glucose to fructose by human placental tissue. Compt. rend. Acad. sc. *232*:1254-56, 1951 (*Abstr. from* Chem. Abstr. *45*:5786, July 10, 1951).

Aqueous extracts of fresh or acetone-dried placenta are capable of phosphorylating glucose and of converting

glucose 6-phosphate to fructose 6-phosphate. An alkaline phosphatase which hydrolyzes hexose phosphate esters also is present in the extracts. These normal mechanisms are responsible for converting the glucose of the maternal blood to the fructose of the fetal blood.

WAKELEY, J. C. N. *(Dept. of Anatomy, Univ. of London at King's Coll):* Annular pancreas. Lancet 2:811-13, November 3, 1951.

A case of annular pancreas is reported in which the presenting symptom was one of indigestion. Partial resection was performed with a satisfactory postoperative result, the patient being free of symptoms for ten years. The abnormal anatomy, pathology, clinical findings, and treatment are briefly discussed.

WALKER, J. W.; AND MAYER-GROSS, W. *(Dept. of Clin. Res., Crichton Royal, Dumfries)*: A study on the hyperglycemic factor in the urine of psychotics. Brit. J. Exper. Path. 32:51-57, April 1951.

The presence of a hyperglycemic agent in the urine of certain psychotics has been confirmed. It has been shown that this agent consists of two fractions. The first fraction—a weaker, more quickly acting agent—has been shown to consist of the salts of uric acid. It has been shown that the activity of the stronger, more slowly acting agent is associated with the amino acid content of the extract. The identity of this second factor is discussed.

WATSON, E. M.; AND THOMPSON, MARGARET W. *(Univ. of Western Ontario, London; Univ. of Alberta, Edmonton):* Heredity and diabetes. Am. J. Digest. Dis. 18:326-29, November 1951.

Although diabetes mellitus shows a marked familial tendency, the exact mode of inheritance of the disease has not as yet been determined completely, chiefly because of the absence of full concordance between the diabetic genotype and phenotype. The percentage of cases with positive family histories of diabetes varies inversely with the age at onset of the disease. The age at onset is earlier in those cases with positive family histories of diabetes than in those without such family histories and is especially early in those with bilateral family histories. On the whole, the available evidence favors the hypothesis that diabetes is inherited as a recessive. The age at onset of the disease is positively correlated in sibs but not, or only slightly, correlated in parent-offspring pairs. There is conflicting evidence as to whether diabetes is more likely to appear in the like-sexed than in the unlike-sexed sibs of diabetic propositi; but the present observations suggest that if any such relationship exists, it can be explained on the basis of the preponderance of female diabetics.

WEIL-MALHERBE, H.; AND BONE, A. D. *(Res. Dept., Runwell Hosp., Wickford, Essex, England):* Studies on hexokinase. I. The hexokinase activity of rat-brain extracts. Biochem. J. 49:339-47, August 1951.

The authors studied the reactions occurring in aqueous rat-brain extracts during the phosphorylation of glucose by adenosinetriphosphate (ATP) and the properties of rat-brain hexokinase. Estimation of the Michaelis constant yielded approximate values of 5×10^{-5}M for hexokinase and 7×10^{-4}M for phosphohexokinase. The affinity for ATP was the same for both enzymes. The Michaelis constant in this case was 8×10^{-4}M. A study of the reaction products showed that glucose was quantitatively converted into hexosediphosphate and that glycolysis did not, under the conditions used, proceed beyond the triosephosphate stage. In the initial stages of the reaction some hexosemonophosphate may accumulate, especially when the enzyme is diluted. The brain extracts used contained somewhat variable amounts of apyrase, myokinase, and adenylic deaminase. The activity of myokinase was sufficient to prevent the accumulation of any but small amounts of adenosinediphosphate (ADP). When ADP was used as phosphate donor, the reaction rate was about 30 per cent slower than in the presence of ATP. Because ATP was always present in excess, the activity of myokinase was never a limiting factor in the reaction. The ammonia formation from ATP, in absence of phosphate acceptors, was limited by the activity of adenylic deaminase rather than myokinase. Brain hexokinase was strongly inhibited by hexosemonophosphates. Glucose-6-phosphate was found to be more inhibitory than fructose-6-phosphate, whereas Robison ester has an effect intermediate between the two components. The results suggest that the inhibitory compound is glucose-6-phosphate. The inhibition by hexosmonophosphates was noncompetitive with respect to either glucose or ATP. No summation of initial reaction rates of hexokinase and phosphohexokinase was observed when glucose and hexosemonophosphate were simultaneously

added to brain extract, because hexokinase activity was inhibited in the presence of hexosemonophosphate. The addition of various substances known to have protective or activating effects on enzymes in general and on hexokinase in particular, alone or in combination, had no effect on the hexokinase activity of rat-brain extracts.

WEIL-MALHERBE, H.; AND BONE, A. D. *(Res. Dept., Runwell Hosp., Wickford, Essex, England):* Studies on hexokinase. 2. An activator of hexokinase in erythrocytes. Biochem. J. *49*:348-54, August 1951.

Red blood corpuscles of man and other species were found to contain a factor which increased hexokinase activity of rat-brain extracts and, to a smaller extent, the activity of rat-muscle hexokinase and of purified yeast hexokinase. In the majority of experiments the activity of brain hexokinase was about doubled in presence of the factor, but the highest effect observed was a sixfold increase of activity. The effect on the phosphorylation of fructose by brain extracts was similar to that with glucose. The activity of phosphohexokinase, on the other hand, was unaffected. The activator did not diffuse on dialysis and could not be separated from protein. It is not present in the stroma of the erythrocyte and is not identical with hemoglobin. It is comparatively heat-stable but loses its activity gradually when exposed to temperatures of 80-100°. Even after heating, the activity was associated with coagulated protein. The activating effect cannot be explained by the presence of hexokinase, phosphohexokinase, triosephosphate dehydrogenase, or myokinase in the erythrocyte lysates. A study of the end products of the hexokinase reaction did not reveal any change of reaction mechanisms.

WEIL-MALHERBE, H.; AND BONE, A. D. *(Res. Dept., Runwell Hosp., Wickford, Essex, England):* Studies on hexokinase. 3. An activator of hexokinase in muscle extracts. Biochem. J. *49*:355-61, August 1951.

A nondiffusable activator of hexokinase, similar to or identical with that present in erythrocytes, was found in rabbit-muscle extracts. It was partially purified by fractionation with ammonium sulfate or by isoelectric precipitation at *p*H 5.6. The activator is associated with an enzyme complex containing adenosinetriphosphatase, adenylic deaminase, hexokinase, and phosphohexokinase. Further fractionation showed that the activator is not correlated with the activity of any particular one of these four enzymes. They could be differentially inactivated by a degree of heating which did not materially impair the function of the activator. On addition of increasing quantities of activator to rat-brain hexokinase, the effect reaches a saturation value. With the more active preparations used by the authors, the addition of 0.5 to 1 mg. 3 per ml. was required for maximum effect. The activator is fairly heat-stable but less so than the erythrocyte factor. After coagulation the activity is contained in the supernatant, from which it can be removed by deproteinization. Purified myosin or myokinase had no activating effect on hexokinase. The activator is specific for hexokinase but does not affect phosphohexokinase. On the other hand, hexokinase activity is increased whether glucose or fructose is the substrate; whether the enzyme is derived from brain, muscle, or yeast; and whether it is crude or partially purified. A study of the end products of the reaction offered no explanation for the activating effect. In particular, no indication was found that the effect was due to removal of inhibitory reaction products. The mechanism of the activation is discussed, and two hypotheses are considered: (1) that the activator acts by catalyzing the conversion of hexopyranose to hexofuranose; (2) that the activator acts directly on the hexokinase molecule, possibly as a member of a chain of factors mediating between hormones and enzyme.

WEINSTEIN, A. *(Vanderbilt Univ. Sch. of Med., Nashville, Tenn.):* Coronary thrombosis and diabetes mellitus: The influence of coronary thrombosis on the metabolism of the diabetic patient. Am. Pract. & Dig. Treat. *1*:1233-37, December 1950 [*Abstr. from* Am. J. Digest. Dis. *18*:287, September 1951].

In two cases of diabetes the onset of coronary thrombosis was associated with an unfavorable disturbance in the carbohydrate metabolism. This may occur before the electrocardiographic picture has become diagnostic. The appearance of acidosis or an increase in the severity of the diabetes may herald the beginning of coronary thrombosis.

WEINSTEIN, JACOB J. *(Gallinger Municipal Hosp. and George Washington Univ. Sch. of Med., Washington, D.C.):* Tolerance of human beings to intravenous infusions of fifteen per cent invert sugar. J. Lab & Clin. Med. *38*:70-78, July 1951.

Intravenous infusions of 150 gm. of invert sugar in 1,000 cc. of water at a rate of 1.5 gm. per kg. per hour were given to each of 21 adult ambulatory hospital "normal" patients. An average of 5.5 gm. of total reducing substance was recovered from the urine collected for the entire 4½-hour test period. Fructose excretion averaged 0.6 gm. Seventy-three per cent of the fluid intake was excreted in the urine in the same period. Fructos and glucose levels at the end of the infusion averaged 268 and 33 mg. per cent respectively, and both had returned to the preinfusion levels one hour later. A 10 per cent average hemodilution was found at the completion of the infusion. The author concludes that fructose is more rapidly removed from the blood, is retained in greater quantities, and is more rapidly assimilated by the human body than is glucose when both sugars are given simultaneously at equal rates and in equal amounts as an invert-sugar preparation.

WEST, G. B. (*Pharmacological Lab., Univ. of St. Andrews Med. Sch., Dundee, Scotland*): Insulin and the supraenal gland of the rabbit. Brit. J. Pharmacol. 6:289-93, June 1951.

When insulin is injected into the rabbit in sufficient amount, the activity present in the suprarenal medulla first increases and then declines. The increase occurs during the first two hours after injection, and the fall is evident after three hours. The minimum value is reached at about four hours, and recovery has taken place by the sixth hour. During the first two hours after injection of insulin, noradrenaline in small amounts may appear in the extract of the suprarenal gland. At all other times the gland contains only adrenaline. If noradrenaline is a precursor of adrenaline in the suprarenal gland of the rabbit, then methylation to form adrenaline occurs rapidly, even in the exhausted gland.

WICK, ARNE N.; AND DRURY, DOUGLAS R. *(Scripps Metabolic Clin., La Jolla, and the Dept. of Physiol., Univ. of Southern California, Los Angeles):* Does concentration of glucose in extracellular fluid influence its utilization by the tissues? Am. J. Physiol. *167*:359-63, November 1951.

In experiments designed to study the relative significance of the extracellular fluid concentration of glucose and of cellular metabolic activity upon the utilization of glucose, the authors measured the glucose disappearance and glucose combustion rates, using uniformly labeled C^{14} glucose, in eviscerated rabbits—four at hyperglycemic levels, three at normoglycemic levels, and one at a normoglycemic level with insulin. Their results indicated that at high blood-sugar levels there may be in the eviscerated animal a small increase in glucose disappearance over that seen at a normal blood-sugar level. In contrast, insulin brings about a marked increase in disappearance and combustion with the blood sugar maintained at normal levels. The effects of insulin cannot be simulated by increasing the plasma glucose concentration even to 1,000 mg. per 100 cc.

WICK, ARNE N.; AND DRURY, DOUGLAS R. *(Scripps Metabolic Clin., La Jolla, and the Dept. of Physiol. Univ. of Southern California, Los Angeles):* Action of insulin on permeability of cells to sorbitol. Am. J. Physiol. *166*:421-23, August 1951.

The authors administered C-14-labeled sorbitol to nephrectomized, eviscerated rabbits and determined its dilution by body fluids before and after insulin administration. Their results showed that sorbitol has a volume of distribution in the extrahepatic tissues corresponding to the extracellular compartment. The distribution is not increased by insulin administration. Since sorbitol does not enter the cell either with or without insulin action, it is suggested that entrance into the cell is dependent on an enzyme mechanism and not a physical one, such as permeability.

WICK, ARNE N.; DRURY, DOUGLAS R.; AND MACKAY, EATON M. *(Scripps Metabolic Clin., La Jolla, Calif., and Dept. of Physiology, Univ. of Southern California, Los Angeles):* Effect of insulin on volume of distribution of glucose. Am. J. Med. *10*:778, June 1951.

The glucose space of eviscerated rabbits was reported on previously and shown to be approximately 26 per cent of the body weight. This value is similar to that of other substances which are distributed in the extracellular compartment. One theory concerning the action of insulin is that it increases the volume of glucose distribution. The authors investigated this possibility, using glucose uniformly labeled with carbon-14. Known amounts of glucose were injected while the animal was under the influence of insulin. The results show that the volume of distribution of glucose was not increased by the insulin administration. The disappearance rate of glucose was found to be greatly increased.

WIELE, H.; GERLICH, N.; AND MERTENS, H. *(Bielefeld, Germany):* Proof and detection of insulin adulteration. Arzneimitt. Forsch. *1*:115, June 16, 1951.

The polarographic examination for proving insulin adulteration is suitable even in the presence of organic additions, so that in most instances biological examination is unnecessary. With inorganic additions, the polarography of the insulin specimen under examination leads to proof because ammonia ions in the basic solution are always present in much greater number than all other ions possibly introduced through adulteration. Biological examination is necessary, however, when proof of the biological effectiveness is required, because even biologically inactive insulin still shows a distinct polarogram which cannot be differentiated from that of active insulin.

WILENS, SIGMUND L. *(Dept. of Pathology, Bellevue Hosp., and New York Univ. Coll. of Med., New York):* The experimental production of lipid deposition in excised arteries. Science *114*:389-93, October 12, 1951.

An experimental study of the filtration properties of excised human arteries confirmed Anitschkow's concept of an outward fluid passage through the arterial walls. Within the range of filtration pressures tested (20 to 320 mm. Hg), large molecular substances did not readily enter the arterial intima, but 2 to 38 per cent of the cholesterol and a small proportion of the protein in the serum were deposited intramurally.

Sudan III stains revealed that the deposited lipid material spread uniformly throughout the entire thickness of the intima in some instances and was concentrated in others at the internal elastic lamella, which appeared to act as an effective barrier against the further penetration of lipid material. After prolonged high pressures, lipid was impregnated throughout the media. It is suggested that the filtration of serum through artery walls under the conditions of the experiments provides direct and substantial evidence in favor of the filtration theory of lipid deposition in atherosclerosis.

WILSON, D. R. (*Edmonton*): Electroencephalographic studies in diabetes mellitus. Canad. M. A. J. 65:462-65, November 1951.

Three cases of labile diabetes are presented in which control was entirely unsatisfactory and was incompatible with a normal life outside the hospital. Abnormal electroencephalograms were found in all instances. Prior to the institution of anticonvulsant therapy, these patients presented extremely labile diabetes, characterized by frequent reactions, uncontrollable glycosuria, and evidence of personality changes. The institution of anticonvulsant therapy resulted in a marked improvement and enabled these individuals to lead a relatively normal life.

WILSON, JAMES L.; AND MARKS, JOSEPH H. *(New Eng. Deaconess Hosp., Boston):* Calcification of the vas deferens: Its relation to diabetes mellitus and arteriosclerosis. New England J. Med. *245*:321-24, August 1951.

Sixty cases of calcification within the walls of the vas deferens are reported. This unusual condition was associated with diabetes mellitus in 56 cases. Calcification was first noted within the vas deferens by x-ray after an average duration of 18.3 years of diabetes. It is the authors' opinion that calcification within the vas deferens represents a relatively specific degenerative complication of diabetes.

WILSON, JAMES L.; ROOT, HOWARD F.; AND MARBLE, ALEXANDER *(New Eng. Deaconess Hosp., Boston):* Diabetic nephropathy. New England J. Med. *245*:513-17, October 4, 1951.

The term "diabetic nephropathy" is favored for the renal disease of mixed etiology seen only among patients with diabetes. It occurs at all ages, but affects most frequently patients in their thirties and forties with severe, poorly controlled diabetes of long duration. The chronologic development of the clinical manifestations of diabetic nephropathy includes albuminuria, increased index of capillary fragility, retinal hemorrhages, peripheral edema, hypertension, and azotemia. Death most commonly occurs from uremia, but at times is the result of myocardial infarction, congestive heart failure, or cerebrovascular accident.

Manifestations of diabetic nephropathy were shown by 62 patients (25 per cent) among a group of 247 young patients with severe diabetes of 10 to 34 year duration, with onset at the ages between 18 months and 30 years. Among the total group of 247 patients, there were 37 who had adequately controlled their diabetes (excellent or good control) by attention to a program that included early and continued use of insulin, careful measurement of a planned diet, medical examination, and daily urine tests, with adjustment of diet and insulin to secure sugar-free specimens. Not

one of these had developed nephropathy at the time of the study.

WOLLMAN, S. H.; AND SCOW, R. O. *(Nat. Cancer Inst. and Nat. Inst. for Arthritis and Metabolic Diseases, Bethesda, Md.):* Effect of hypophysectomy and adrenalectomy on the succinoxidase activity in the livers of alloxan diabetic rats. Endocrinology *49*:105-09, July 1951.

Normal, alloxan diabetic, adrenalectomized, hypophysectomized, adrenalectomized diabetic, and phypophysectomized diabetic rats were maintained on a bread and milk diet. All adrenalectomized rats were given 1 per cent saline as drinking water. Livers were examined for nitrogen content and succinoxidase activity. The liver nitrogen of the unfasted alloxan diabetic rat was elevated 30 per cent above normal, though the percentage of water was normal. Liver succinoxidase activity was 70 per cent above normal per unit of fresh weight, but only 25 per cent above normal per milligram of nitrogen. Per cent liver nitrogen and liver succinoxidase were brought down to that of the corresponding nondiabetic controls by adrenalectomy or hypophysectomy. The livers of normal and adrenalectomized rats have the same nitrogen content and succinoxidase activity per gram of fresh weight. The livers of hypophysectomized rats have slightly elevated nitrogen content and an elevated succinoxidase activity which is proportional to the elevation in liver nitrogen.

YANG, TSCHAU-TJIAN: Photometric studies on the permeability of red blood cells to sugar. Schweiz. med. Wchnschr. *80*:1157, 1950 [*Abstr. from* Deutsche med. Wchnschr. *75*:1739, December 22, 1950].

The permeability of erythrocytes to sugar is the same in diabetics as in normal subjects. Glucose permeability depends on temperature, being low at 4 to 18°C. and high at 30 to 40°C. Increase in permeability within these limits is directly proportional to rise in temperature. Insulin effects an increase in permeability to glucose in vitro as well as in vivo. In the rabbit, erythrocytes bind sugar only in the presence of insulin. Thyroxin and physostigmine (1:360,000) increase permeability in the human. Atropine (1:360,000) decreases permeability, as does vitamin P (citrin) (1:36,000).

YENER, M. S. *(Paris):* Two cases of diabetes complicated by the Kimmelstiel-Wilson syndrome. Semaine D. Hôp. Paris *27*:109-10, 1951 [*Abstr. from* Excerpta Med. (Int. Med.) *5*:1118, August 1951].

The clinical picture and theories of the pathogenesis are discussed.

YOUNG, B. A.: Potassium therapy in diabetic coma. Pharm. J. *166*:288, April 21, 1951.

The author suggests that when the disordered carbohydrate metabolism in diabetic coma is corrected with insulin, salt, and glucose administration, the electrolyte balance may be disturbed with respect to potassium and phosphorus. The administration of potassium and phosphate is suggested to reduce this still frequently fatal complication of diabetes mellitus.

YOUNG, F. G. *(Dept. of Biochemistry, Univ. of Cambridge, Cambridge, England):* The experimental approach to the problem of diabetes mellitus. Brit. M. J. *2*:1167-73, November 17, 1951.

The author discusses his own and other research regarding the role of the pituitary in diabetes mellitus. It is felt that the evidence at our disposal at the present time allows us to associate growth, including fetal growth, and milk production as phenomena whose development is stimulated by growth hormone. Excessive pressure on these processes in circumstances in which the physiological stimulus cannot fully or properly realize itself can lead to the pathological outcome of diabetes, a condition in which the material preserved from oxidation but not utilized may be excreted in the form of sugar. In the human being a slightly excessive rate of secretion of growth hormone, insufficient to cause overt signs of acromegaly but lasting a long time, might lead to a prolonged but not excessive restraint upon the processes of carbohydrate and protein catabolism and oxidation, combined with the increase in appetite characteristic of growth hormone activity, so that diabetes ultimately develops. In growth hormone we have a substance that may well be of importance in in the etiology of a serious proportion of cases of human diabetes mellitus.

ZAJAC, LEON: Two cases of benign islet-cell tumor of the pancreas. Polski przegl. chir. *22*:1055, 1950. [*Abstr. from* Surg., Gynec. & Obst., Internat. Abstr. Surg. *93*:462, November 1951].

Two cases of benign islet-cell tumors given surgical treatment are reported. The author also mentions 43 cases which he found in the literature available to him. Thirty-nine of these are analyzed in tabular form.

EDITORIALS

THE INSULIN CONTENT OF PANCREAS

At various times, starting soon after insulin was isolated, we have been interested in the amount of insulin in degenerated pancreas from the dog, in normal dog pancreas, fetal calf pancreas, normal beef pancreas, commercial pancreas from many species, in normal human pancreas and in pancreatic islet tumors. The variations in insulin content of beef pancreas with the age of the animal, the effect of starvation and of various diets on the insulin extractable from pancreas, and the effect of diabetogenic hormones from pituitary, adrenal or thyroid glands, of alloxan and related compounds, and of insulin itself, have all been investigated. In all these studies it has been fully realized that the amount of insulin extractable is the resultant of a number of factors and that we have little knowledge of most of them. The rate and amount of insulin formed in the islet cells, the rate of destruction in the islet cells (if this occurs), and the rate of liberation of insulin into the blood may be independent variables. But in spite of these reservations the data obtained have been stimulating and, when considered in relation to the metabolic state of the owner of the pancreas, highly informative. Of course we need to have accurate estimations of blood insulin routinely available, but then we would wish to know the rate of insulin secretion, the rate of its fixation, inactivation or destruction by blood or other tissues, and the rate of its excretion by the kidneys. We are progressing, and it is wise to consider the information we have available.

The extractable insulin of pancreas in animals is reduced by certain periods of fasting, by feeding a diet very rich in fat, and by giving a great excess of insulin. The fact that a diabetic type of glucose tolerance curve appears concomitantly with the reduction in insulin content suggests that one of the causes of the disturbed carbohydrate utilization is a decreased rate of liberation of insulin. We know that this is not the only cause. When pituitary extracts rich in growth hormone are given in large doses to susceptible dogs, the insulin content of the pancreas sinks almost to zero. The same is true after complete alloxanization. This state of affairs, considered in conjunction with the destruction of the beta cells and a severe diabetes which can be eliminated by the amount of insulin which we estimate is normally secreted, probably means that no insulin was being liberated. Tumors of the beta cells may yield 250 units of insulin per gram in contrast to 2 or 3 units from normal pancreas. This high value approximates the insulin content of pure islet tissue. The presence of insulin-rich tumors has been associated with

*The term "extractable insulin" is more exact and therefore preferable to "insulin content," but when the content has been estimated using the best available method of extraction, and the reader keeps this in mind, the two terms are interchangeable.

tne clinical signs indicative of a high rate of insulin liberation, which may be restored to normal by removal of the offending cells. It is probably the absence of control of insulin liberation in the cells of the tumor rather than the increased number of islet cells which results in excess secretion of insulin.

It is entirely possible that a high rate of liberation of insulin might *reduce* the amount in normal pancreas.† There is some indirect but no direct evidence that this occurs. We do not know within what ranges the tremendous gradient between insulin content of beta cells and insulin content of blood, conservatively estimated as one million to one, is permitted to vary under normal or abnormal conditions. We know very little about the factors which control insulin formation. The molecule is presumably built up, in part at least, from dietary amino acids.

A great excess of sugar over a prolonged period may, in cooperation with normal or perhaps raised levels of diabetogenic substances, lead to the destruction of the insulin-producing mechanism in certain species of animals. A rise in sugar content of the blood perfusing the islands of Langerhans causes an outpouring of insulin. Diabetogenic pituitary extracts increase the insulin content of the pancreas in certain types of rats, but this has never been detected in the adult dog, whose islands are much more sensitive to the destructive effects of these substances. A rise in insulin content of pancreas might occur in the dog but escape detection by present methods. There are plenty of proliferative changes in islands, ducts, and acini in the early stages of pituitary administration. A temporary increase in the rate of liberation of insulin might be accomplished, without change in content, by an increase in the rate of production which corresponds precisely with the raised output. There might be an immediate fall in the insulin content of dog's pancreas when diabetogenic substances are given. A slight and transitory one would not be detected. We know that the decrease becomes very definite as the injections are continued but at this later stage there is no evidence of increased insulin output. This could be occurring and might easily be masked by the excess of the antagonistic substances. Blood insulin determinations will help to reveal the facts during this period when cessation of the injections of pituitary extract is followed by return of pancreatic insulin to normal levels.

If the level of blood insulin were the main factor controlling the insulin content of pancreas, one would expect that administration of an excess of insulin would lead to a fall in the level in pancreas. This effect is actually very well marked. The insulin content of pancreas may be reduced to a fraction of the normal level by giving large doses of insulin. One might expect also that hypo-insulinemia would lead to an increased rate of production and output of insulin. There are several great difficulties in the way of investigating this matter. The blood sugar rises when we deprive the animal of insulin unless the need for insulin is reduced by removal of opposing hormones. The increased sugar may be the stimulus rather than the decrease in insulin. Both blood sugar and blood insulin may prove to be factors regulating the output of insulin. We are just at the beginning of determinations of blood insulin (Bornstein and Lawrence).

The paper in this issue by Wrenshall, Bogoch and Ritchie records the results of by far the most thorough and comprehensive study of the insulin content of *human* pancreas as yet made. The actual figures for extractable insulin may change somewhat—there might even be a combined form of insulin which is not completely released by present methods. But this paper lays a firm groundwork for future developments. It answers some of the questions which have perhaps made other groups hesitate to enter the field. The actual findings speak for themselves and need little further comment. "Growth onset" diabetes and the form which waits for maturity, certainly lead to different levels of insulin storage in the pancreas. This does not prove, however, that the manner of production of the two types of diabetes is different. Something halts the decrease in insulin storage in the "maturity onset" group. Diabetic coma levels these differences and even the "maturity onsets" lose all their pancreatic insulin. Would storage of insulin have been restored to the pre-coma value if recovery from coma had occurred? How early in their diabetes do the "growth onset" types lose all their pancreatic insulin? There is some clinical evidence on this point which can perhaps be correlated with values for extractable pancreatic insulin.

In the future much more data on human pancreatic insulin will be secured. Insulin values in blood, at present of qualitative significance, will acquire greater reliability. It will be possible also to estimate in blood the amounts of each of the hormones which may oppose the anabolic effects of insulin. The physiological activities of liver and muscle cells obtained from patients by safe microbiopsies will be studied in the light of the

†The earlier work on Insulin Content of Pancreas was reviewed by Dr. R. E. Haist in Physiological Reviews, October 1944.

"spectrum" of their blood hormones. The pathologist using the refined histochemical methods of the day will report on the biopsy specimens and add his findings to the many which the clinician will evaluate.

—CHARLES H. BEST, M.D.

DIABETES DETECTION DRIVE—1951

Under the capable, enthusiastic and discriminating direction of Dr. John A. Reed of Washington, Secretary of the American Diabetes Association, the fourth annual campaign to discover unrecognized diabetes was launched in November 1951. A full week of national and local activities inaugurated a Drive which will continue on a modified scale throughout the year. Initiated by the American Diabetes Association in 1948, this campaign has broadened in scope and improved in effectiveness each year. The one this year is the largest and best yet.

Several important objectives are accomplished by the American Diabetes Association's detection activities. A substantial number of unknown cases is found. Many patients known to be diabetic are inspired to stop neglecting themselves. Perhaps of even greater importance, diabetics and the interested general public alike learn to understand diabetes better as a result of sound and authoritative information released through public channels during the Drive. Employment, insurance and other public attitudes are cultivated more intelligently thereby. Regional diabetes units are given an active and specific outlet for their energies in behalf of diabetics. Finally, the American Diabetes Association grows in prestige and in public confidence in direct proportion to the quality and amount of constructive accomplishment achieved in these and other areas by the campaign.

The medical profession must now be fully aware of the fact that the Association's basic philosophies in the conduct of this Drive are: help for all diabetic patients in all conceivable ways; active participation and direction by the profession; and avoidance of direct appeal for funds from the general public. The dignity and public trust resulting from these policies are assets which should be prized highly by everyone connected with the Association.

Many different patterns of performance in the execution of this work have evolved in various parts of the country. No standardized method has been accepted so far. Publicity efforts, urine testing procedures, follow-up diagnostic work, reporting of results and referral of patients for care are handled by a variety of different mechanisms, especially at local levels. This is as it should be, for the present at least. The best methods will emerge in time, with the Association acting as referee and clearing-house for the exchange of useful information. Probably a standardized method should never be adopted as long as active work is conducted independently by local diabetes units, each with its own problems and personnel. In the meantime the resourcefulness and imagination of many people working in a fertile field of common interest will perfect methods and mechanics more rapidly than a small national group could ever do.

The multitude of unselfish, crusading volunteers all over the country are to be congratulated for their interest, resourcefulness and devotion. Dr. Reed, and Dr. Howard F. Root who preceded him as commander of all detection activities, have won the admiration and confidence of the Association and the public for the energetic and wise manner in which the Drives have been conducted. The campaigns stand as imposing monuments of Association achievement.

—ARTHUR R. COLWELL, M.D.
President, American Diabetes Association

EMERGENCY MEDICAL CARE OF DIABETICS

Publication of the official Statement of the American Diabetes Association's Committee on Emergency Medical Care in *The Journal* of the American Medical Association in its December 1, 1951 issue[1] places the studies and plans of this Committee at the disposal of the medical profession, the Civilian Defense Administration and diabetics themselves. These plans were formulated as the result of over a year and a half of careful study intended to protect the interests of this large segment of population in event of war or any other major catastrophe. The emergency procedures recommended have been worked out in cooperation with the Federal Civilian Defense Administration and other responsible government agencies, the American Medical Association, and similar interested organizations. These recommendations should now be incorporated into all national and local programs designed to protect our civilian population in time of national emergency.

An abridgment of the original report appeared in the first issue of *Diabetes*,[2] together with a proposed handbill for general distribution, "The Diabetic and the Atomic Bomb." These simplified instructions to the patient should be reproduced by all responsible agencies

and broadcast so that every diabetic has a copy at hand to guide him in case of sudden emergency.

The report of the Committee also urges an educational and training program for diabetics in preparation for a possible attack, and the incorporation into the civil defense programs of the skills of graduate dietitians, a group that would play a vital part in maintaining the nutrition of the injured persons who would be too sick to feed themselves. Dietitians, nutritionists and home economists who have experience in quantity feeding would be a nucleus for training diabetics and other people so that they could assume the responsibilities of feeding large masses of the population.

The American Dietetic Association and the American Home Economics Association have endorsed the Red Cross Food and Nutrition Service registry of nutritionists for recruiting professional dietitians, nutritionists and home economists; this institution can serve as another resource for local civil defense organizations. Ellen C. Ruthman is Assistant National Director of the American Red Cross Food and Nutrition Service. In the *Red Cross Magazine* for November 1951, she outlined the contribution this group can make to the civil defense effort. An important part of her statement is her suggestion that it is now up to the local Red Cross chapters to take full advantage of the talent waiting on their doorsteps.

REFERENCES

[1] Emergency medical care of diabetics in civilian defense. J.A.M.A. *147*:1350-54, Dec. 1, 1951.

[2] The diabetic and civilian defense. Diabetes *1*:78-82, Jan.-Feb. 1952.

THE DISCIPLINE OF SCIENCE

To the physician particularly, a scientific discipline is an incalculable gift which leavens his whole life, giving exactness to habits of thought and tempering the mind with that judicious faculty of distrust, which can alone amid the uncertainties of practice, make him wise unto salvation. For perdition inevitable awaits the mind of the practitioner who has never had the full inoculation with the leaven, who has never grasped clearly the relations of science to his art, and who knows nothing and perhaps cares less for the limitations of either.

—From *Aequanimatis and Other Addresses,* by Sir William Osler. Blakiston and Company, Philadelphia, 1904.

BOOK REVIEWS

TEXTBOOK OF ENDOCRINOLOGY. *Edited by Robert H. Williams, M.D., Executive Officer and Professor of Medicine, University of Washington Medical School, Seattle. Cloth. $11.00. Pp. 793. Illustrated. W. B. Saunders Co., Philadelphia and London, 1950.*

The best medical textbooks are usually those which are based upon the personal experience of the authors. In recent years clinical endocrinology has become so broad in scope that a single author can no longer write authoritatively on all its aspects. Consequently, multiple authorship of a textbook of endocrinology by men who have expert knowledge of the various subdivisions of the field has become essential.

This volume on clinical endocrinology illustrates the advantages of multiple authorship. The contributors are men who for the most part are experts on the subjects assigned to them. Robert H. Williams writes on "General Principles of Endocrinology," the "Pituitary," the "Thyroid," and "Laboratory Diagnostic and Assay Procedures;" the late Edwin J. Kepler and William Locke on "Chronic Adrenal Hyperfunction;" George W. Thorn and Peter H. Forsham on "Adrenal Cortical Insufficiency;" John Eager Howard and William Wallace Scott on "The Testes;" George Van S. Smith on "The Ovaries;" George W. Thorn and Peter H. Forsham on "The Pancreas and Diabetes Mellitus;" Edward C. Reifenstein, Jr., on "Diseases of the Parathyroid Glands;" Lawson Wilkins on the "Influence of the Endocrine Glands Upon Growth and Development;" Harry B. Friedgood on "Neuroendocrine and Psychodynamic Aspects of the Endocrinopathies;" and L. H. Newburgh on "Obesity." The assemblage of endocrine material by these authors constitutes a textbook which is authoritative, practical and thorough.

The chapter on diabetes mellitus by Thorn and Forsham is well organized and makes effective use of headings and sub-headings. Fundamental aspects of endocrinology and metabolism in relation to diabetes, as well as purely clinical topics, are taken up in systematic fashion. The authors' style of writing is interesting, readable and usually (but not always) clear. Lack of clarity is apparent in the discussion of the use of insulin for the diabetic patient who must undergo surgery. It is stated that half the daily requirement for insulin may be given preoperatively and half postoperatively, and no more insulin need be given that day. If this advice were applied to a patient with severe diabetes which had been treated with soluble insulin, there would be grave danger of acidosis late on the first postoperative day owing to deprivation of insulin. Undoubtedly the authors intended some restriction on the use of this method of treatment.

Other criticisms of this chapter are largely concerned with details rather than with the over-all presentation of the subject. Thus, the brief paragraph on lipemia retinalis on page 484 fails to mention that this interesting condition occurs chiefly in diabetic acidosis and coma. Likewise, table 36 on page 544 can be interpreted to mean that loss of consciousness occurs in 58 per cent of instances of hypoglycemia and deep coma in 40 per cent. The significance of these and other data in this table is not clear, and is not adequately explained in the text. In spite of a number of similar objections, this is a good and thorough chapter on diabetes. It should be noted that the subject of hyperinsulinism is not taken up in this or in any other chapter.

The chapters on the pituitary and thyroid written by the editor himself are based on wide experience in these fields. Illustrations of good quality and well-planned tables enhance the material presented in the text. The propri-

ety of using certain colored illustrations provided by a pharmaceutical company dealing in endocrine products can be questioned, albeit these illustrations are of superior quality.

Chapters on the adrenals, testes and ovaries are all well presented by highly competent authorities. The material on chronic adrenal hyperfunction is interestingly and lucidly written by Kepler and Locke and is exceptionally well illustrated. The discussion of adrenal cortical insufficiency by Thorn and Forsham is expertly handled. Howard and Scott include appropriate comments on the rarity of the spontaneous male climacteric in their chapter on the testes. Testicular biopsy as a diagnostic method receives only brief consideration. Smith's chapter on the ovary is well done from both the physiologic and clinical points of view. As might be anticipated, certain points are discussed on which there is no general agreement (for example, menstrual toxin as an explanation for premenstrual nervous tension).

Reifenstein's chapter on the parathyroid glands is based largely on the author's extensive experience in this field during his association with Albright at the Massachusetts General Hospital. It would be difficult to improve on this chapter. Likewise, the chapter by Wilkins on growth and development is of the highest quality. The tables include many valuable data on normal growth and development. The chapter on obesity by Newburgh provides a theoretical and practical discussion of this common problem which is both sound and conservative. The idea that obesity is not basically an endocrine problem in most instances is implicit in the discussion.

At the present stage of development of clinical endocrinology the inclusion of a chapter on the neuroendocrine and psychodynamic aspects of the endocrinopathies is probably justified. However, much of the material in Friedgood's chapter on this subject has a less sound experimental and clinical basis than most of the other material in the book. The reviewer was impressed that the length of this chapter and the number of references are out of proportion to the amount of substantial knowledge in this field. Some of the author's opinions and speculations are distinctly out of line with established thought in endocrinology.

The final chapter on "Laboratory Diagnostic and Assay Procedures" by Williams contains a good fund of concise information for those who want to know the basic principles of hormonal assays and other laboratory procedures which are employed in clinical endocrinology.

This is clearly an outstanding book on clinical endocrinology which deserves wide reading by students and physicians.

LOW-SODIUM DIET: A MANUAL FOR THE PATIENT. *By Thurman R. Rice, M.D., Professor of Public Health, Indiana University School of Medicine, Indianapolis, Indiana. Cloth.* $2.75. *Pp.* 103. *Lea & Febiger, Philadelphia,* 1951.

The author was placed on a low-sodium diet and wrote the book to explain how to follow it successfully. "It is the author's purpose to set forth the low-sodium diet; he makes no attempt to tell *when* it should be used; or in any way to recommend its use or its discontinuance. At all times, it is recommended that the patient using such a diet keep close to his physician for diagnosis, treatment and direction. The author, though he is a physician, makes no claim to being an authority on the subject of circulatory or other disease requiring low-sodium diet, but he is fortunate in having the advice of those who are entitled to be regarded as such. He wishes to make it very plain that this manual is not in any way intended to replace the counsel of the physician in charge of the particular clinical case."

The author achieves his goal of writing instructions in a manner simple, practical and useful. The scope of the volume is shown by the titles of certain chapters, including, "The Forms of Sodium Found in Food, Where and How Does One Get Low-Sodium Foods," "Originality and Ingenuity in the Low-Sodium Diet," "The Use of Sodium Menus," "Food Lists Rated by Content of Native Sodium," "Typical Food Charts for Study and Consideration," and "Water Supplies in Relation to Sodium Content." The appendix gives a list of companies producing acceptable "sodium-low" foods.

The book should be helpful to the physician, to the patient for whom a low-sodium diet is recommended, and also to the housewife who undertakes the responsibility of preparing his food.

RICE, DIETARY CONTROLS AND BLOOD PRESSURE WITH RECIPES AND MENUS. *By Frances I. Seymour, M.D.* Cloth. $2.95. Pp. 206. Froben Press, New York, 1951.

After personal experience with the rice diet for the treatment of hypertension, Dr. Seymour, Medical Director of the National Research Foundation for Fertility, decided to write a book to give information to others. "In that way, every sufferer everywhere would have the benefit of what I had learned." Although explanation of the rice-fruit low-sodium diet is the apparent objective, the discussion wanders far afield. Nearly 100

pages of the book appear to be identical, for the most part, with the contents of ordinary cook books; including sections dealing with cookery processes, jelly making, the canning of tomatoes, and the drying of fruits and vegetables. The chapter devoted to laboratory tests tends to be equally irrelevant; it includes a page and a half on a test for glycosuria and sugar tolerance tests.

The critical reader of the book will be impressed with the large amount of irrelevant material but will consider it harmless until he comes to the chapter entitled, "The Diabetic and the Rice Diet." This consists almost entirely of a communication from "a well-known dietitian and laboratory researcher." The following statement appears: "If you are a diabetic—no matter what your age, duration of your disease, or degree of its severity—and are experiencing symptoms or signs of mounting blood pressure, which does not yield to a modified salt-poor, fat-poor diet, then the rice diet is designed for you. If your physician informs you that because of your diabetic condition, the rice diet is *not* indicated in your case, then he is either misinformed or uninformed, and should take steps to correct both." This book cannot be recommended.

ENDOCRINE FUNCTIONS OF THE PANCREAS. *By Bernard Zimmerman, M.D., Department of Surgery, University of Minnesota. Cloth. $2.50. Pp. 82. Illustrated. Charles C. Thomas, Springfield, Ill., 1952.*

The author has undertaken to present a collection of past and recent physiological information in regard to the pancreas. Among over 250 references cited, the two referring to his own studies show his interest in alloxan diabetes and the hyperglycemic hormone of the pancreas. Short chapters deal with the history of the pancreas as an organ of internal secretion, the nature of insulin, the metabolism in diabetes and the action of insulin, the regulation of the internal pancreatic secretion, special problems in lipid metabolism, and the hyperglycemic factor. The author achieves his goal of presenting an introduction to the absorbing field of scientific literature on the subject.

BACK COPIES WANTED

The National Office is completely out of stock on Volume 1 of the Proceedings *of the American Diabetes Association, dated 1941, and would like to purchase a limited number of copies of this book. Five dollars will be paid for every copy purchased.*

These volumes are required to complete sets of the Proceedings *ordered by libraries and by individual physicians. Anyone who has a duplicate of Volume 1, or who for some reason no longer has use for his own copy, will do the Association a real service by sending the book to Mr. J. Richard Connelly, American Diabetes Association, 11 West 42nd Street, New York 36, N. Y. Payment will be made within a week or so after each volume is received.*

ORGANIZATION SECTION

Preliminary Program

1952 Scientific Sessions

TWELFTH ANNUAL MEETING

AMERICAN DIABETES ASSOCIATION

THE DRAKE HOTEL, CHICAGO, ILLINOIS

JUNE 7 AND 8, 1952

A tentative schedule of papers which are to be presented at the Scientific Sessions of the Association's Twelfth Annual Meeting appears below. This schedule is subject to further amplification and revision; the final program will be published in the May-June issue of this Journal.

DAVID ADLERSBERG, JOHN J. BOOKMAN, STANLEY R. DRACHMAN, AND LOUIS E. SCHAEFER:

Steroid Diabetes During Cortisone and ACTH Therapy

JOSEPH H. BARACH AND ALEXANDER LOWY:

Atherosclerosis, Arteriosclerosis and S. F. Fat Particles. Preliminary Report on 1000 Cases of Diabetes Mellitus.

CHARLES H. BEST:

Insulin. (Banting Memorial Lecture.)

JOSEPH H. CRAMPTON:

The Role of Potassium in the Reduction of Mortality from Diabetic Coma.

EDWARD S. DILLON, RUSSELL RICHARDSON, KATHARINE R. BOUCOT, DAVID A. COOPER, AND PAUL MEIER:

Tuberculosis Among Diabetics. The Philadelphia Survey.

HYMAN ENGELBERG, HARDIN B. JONES, AND JOHN W. GOFMAN:

Serum Lipids and Lipoproteins in the Kimmelstiel-Wilson Syndrome.

HARRY W. FARRELL, ALBERT M. HAND AND ALVAH L. NEWCOMB:
Infantile Diabetes.

GEORGE M. GUEST, BRUCE MACKLER AND HARVEY C. KNOWLES, JR.:
Effects of Acidosis on Insulin Action and on Carbohydrate and Mineral Metabolism.

LAWRENCE E. HINKLE, JR., AND STEWART WOLF.:
Changes in Blood Glucose in Response to Stress and Their Relevance to Diabetes Mellitus.

DWIGHT J. INGLE:
Some Further Studies on the Relationship of Adrenal Cortex Hormones to Experimental Diabetes.

JOSEPH L. IZZO, DANIEL B. SCHUSTER, AND GEORGE L. ENGEL:
The Electroencephalogram of Patients with Diabetes Mellitus.

NILS KEIDING, GEORGE V. MANN, HOWARD F. ROOT, AND ALEXANDER MARBLE:
The Serum Cholesterol and Lipoprotein Levels in Young Diabetic Patients of Long Duration.

ARNOLD LAZAROW:
Spontaneous Disappearance of Alloxan Diabetes in the Rat After 12-20 Months of the Disease

MAX MILLER, J. W. CRAIG, H. WOODWARD, JR., E. J. OWENS, W. DRUCKER, AND J. MURPHY:
The Metabolism of Fructose in Diabetic Subjects.

JAKOB S. MOLLERSTROM:
Title to be announced.

ROBERT H. TRUEMAN, JOSEPH T. BEARDWOOD, JR., AND JULIUS J. SMITH:
Roentgen Therapy in Diabetic Retinopathy.

L. O. UNDERDAHL:
Multiple Endocrine Adenomas: Report of Eight Cases.

Panel discussions on the following subjects will be presented:

1. *Complications and Sequelae of Diabetes: Relation to Control.*
2. *Factors in the Pathogenesis of Diabetes.*
3. *Diabetic Acidosis and Coma: Prevention and Management.*

Members of the American Diabetes Association are invited to submit questions for discussion by the panels. Address questions to the Committee on Scientific Programs, American Diabetes Association, 11 West 42nd Street, New York 36, New York.

The 1951 Diabetes Detection Drive

A Preliminary Report of
the Committee on Detection and Education
Made at the Interim Meeting of the Council of
the American Diabetes Association
Indianapolis, Ind., January 19, 1952

A full statistical report on the results of the Diabetes Detection Drive during 1951 cannot be given at this time in view of the fact that the official forms presenting data on the Drive have not yet been returned from the County (or District) and State Medical Society Committees on Diabetes. However, it is felt to be both important and timely to present a narrative resume of the activities of the Association in this area so that its entire membership, and the medical profession as a whole, will be appraised of the project and will have some idea of its continuing growth.

There are three major reasons why the American Diabetes Association in 1948 inaugurated a Diabetes Detection Drive and why that Drive has been adopted as a continuing program which is spearheaded annually by a nationally promoted Diabetes Week—the whole activity devoted to an endless search for the "unknown diabetic." First, diabetes as a disease entity is of continually growing importance in our aging population as one of the leading causes of death. Second, several reliable and repeatedly-confirmed surveys have indicated that there are approximately a million persons with undiagnosed diabetes in this country. Third, early discovery and treatment of the disorder should unquestionably help to decrease the number of irreversible complications arising from the disease. Taken together, these reasons constitute a challenging mandate for the continual search for the undiagnosed diabetic by our Association.

Within individual communities the work has been carried out by Committees on Diabetes of the official County and State Medical Societies of the American Medical Association and the local Affiliates of the American Diabetes Association. This year there were exactly 636 county and 30 state Committees on Diabetes, 28 Affiliate and 5 Non-Affiliate Diabetes Associations, and in addition, 170 individual officers of County and State Medical Societies who participated without officially formed Committees on Diabetes. The grand total of all groups and individuals conducting local detection campaigns during the year is 849.

The typical local program involves, from the medical point of view, a screening of individuals by urinalysis or blood test for the presence of an abnormal amount of sugar. Whenever evidence suggestive of the presence of diabetes is found, the individual is notified and is referred for further diagnosis to his own physician. Under certain circumstances physicians are notified rather than individuals; this happens occasionally in programs for screening school children.

The rapid growth in the number of County and State Committees on Diabetes, the tremendous interest in the program on the part of officers of these official American Medical Association organizations, the enthusiastic participation by thousands of individual physicians on the activity in communities throughout the United States and the widespread acceptance of, and interest in, diabetes detection on the part of the public are indisputable evidence not only of the need for such a program but also of its highly effective educational value. The undertaking is, of course, still in a stage of swift development and therefore is confronted with innumerable problems and difficulties. Undoubtedly, a critical analysis of the data to be obtained during the

next few months from the official reports on the Drive will present practical answers to many of these questions.

ACTIVITIES OF THE NATIONAL ASSOCIATION

Drive Materials

To assist these Committees on Diabetes in conducting a successful community Diabetes Detection Drive, the national Association made available the following varied Drive material:

1. PAMPHLETS AND LEAFLETS

What Is the Diabetes Detection Drive?
Organizing a Successful Diabetes Detection Drive.
Finding the Diabetic in Your Community
Diabetes—Its Detection. Its Control (leaflet, new)
How Women Can Help Detect Diabetes (new)
How to Gain the Cooperation of Business and Industry in the Diabetes Detection Drive
How Business and Industry Can Cooperate in the Diabetes Detection Drive
Detecting Diabetes Among School Children
Suggested Medical Procedures and Reporting Methods for Follow-Up (New)

2. POSTER

Have *You* Been Tested for Diabetes?

3. RADIO TRANSCRIPTIONS

30-Minute Dramatizations; 15-Minute Dramatizations; 13-Minute Interviews; Spot Announcements

4. TESTING MATERIALS

Chemicals and supplies for making 1,416,610 individual urine tests distributed on order.

National Publicity

Magazine, newspaper and syndicate publicity on the Drive arranged by the Association was extensive. It is summarized below in two parts, *Professional Relations* and *Lay Publicity*. Space permits only a listing of the names of the media in which special publicity appeared.

PROFESSIONAL RELATIONS

Journal of the American Medical Association; *Postgraduate Medicine; The PR Doctor; Current Medical Digest; Modern Medicine; Medical Economics; Journal of The American Dietetic Association; The American Journal of Nursing; The Journal of the American Pharmaceutical Association; Lab World;* innumerable County Medical Society Bulletins and State Journals.

LAY PUBLICITY

A. Radio (local and national): American Broadcasting Company; Columbia Broadcasting System; Mutual Broadcasting System; National Broadcasting Company
B. Television: American Broadcasting Company; Columbia Broadcasting System; Dumont Television Network (New York and New England); WPIX Television (New York and New England)
C. Newspaper Wire Services, Syndicates and Special Writers: Associated Press; United Press; King Features Syndicate; United Features; Newspaper Enterprise Association; North American Newspaper Alliance; Women's National News Service; syndicated medical columnists; science writers
D. Magazines: *Life and Health; Magazine Digest; Today's Health; Today's Woman; A.D.A. Forecast.* Also innumerable trade journals, house organs and the like
E. Endorsements: from various civic, labor, religious and educational leaders. In particular, the Detection Drive this year received the wholehearted endorsement of the Association of Junior Leagues of America, the American Federation of Labor, and the Congress of Industrial Organizations. The Advertising Council, Inc., has also approved the Drive and listed it in its November-December 1951 *Radio Bulletin.*

FINANCIAL SUPPORT

This program has been made financially possible by funds voluntarily donated for the purpose, as well as by an added amount appropriated by Council action from the General Fund of the Association. Despite the sizable expansion of the program this year, which has involved the publication of three new Drive pamphlets and a new poster, the provision of wider national publicity before and during the Drive, and the making of two financial grants for specific follow-up studies, the Committee has operated entirely within its allotted budget. It has used only funds voluntarily donated for this specific work, with the exception of $500.00 appropriated from the General Fund.

ACKNOWLEDGMENTS

The Committee wishes to express its deep appreciation to Arthur R. Colwell, M.D., President of the Associa-

tion, for his helpful cooperation; to the Council of the Association for its assistance; to the Committee on Purposes and Policies of the Association for its important analytical criticisms. All of these helped to guide the Detection Committee in its efforts to develop a more effective and useful undertaking. The actual functioning of the Committee and the production of the materials necessary for its work would have been to all intents and purposes impossible without the help of Mr. J. Richard Connelly, Executive Director of the Association. To him unlimited credit is due.

Respectfully submitted,

Committee on Detection and Education*
John A. Reed, M.D., *Chairman*

*For a list of the members of this Committee, kindly turn to page 169, this issue of DIABETES. *Ed.*

ASSOCIATION NEWS

INTERIM COUNCIL MEETING

The Council of the American Diabetes Association held its Interim Meeting in Indianapolis on Saturday, January 19, 1952. In addition the Councilors participated in two panel programs for the medical profession and in two lay programs before and after the Interim Meeting.

Two days before the formal Council meeting, the Council members spent the day in Cincinnati as guests of the Council on Diabetes of the Public Health Federation of Cincinnati. Mayor Carl W. Rich proclaimed January 17 "Diabetes Day Observance," and opened the lay meeting, which was held in the afternoon. Dr. Frederick W. Williams of New York was moderator. In the evening a professional panel discussion took place at the University of Cincinnati College of Medicine. Moderator was Dr. Cecil Striker, first President of the American Diabetes Association and this year's President of the Cincinnati Academy of Medicine. During the day Dr. Striker, Dr. Charles H. Best, co-discoverer of insulin, and Dr. Arthur H. Colwell, President of the Association, were on radio and television programs.

Friday morning the members of the Council left for Indianapolis, and in the evening a professional panel discussion was held in the Medical Center Auditorium. The following evening, after the Council had completed its sessions, its members participated in a lay meeting which, like the professional panel of the day before, was sponsored by the Indianapolis Diabetes Association. Dr. John A. Reed of Washington, D.C. presided over both of these meetings.

The following committees of the Association also met during the two-day stay in Indianapolis: the Executive Committee and the Committees on Affiliate Associations, Constitution, Emergency Medical Care, Finance, Membership, Scientific Publications, and Study of Membership Qualifications.

FIRST CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The International Diabetes Federation will hold its first Congress July 7 to 12, 1952, in Leyden, The Netherlands. This international meeting will afford an excellent opportunity for the exchange of clinical and research data, and physicians the world over are invited to attend.

Dr. Elliott P. Joslin has been asked to open the Con-

gress and Dr. Charles H. Best will give the Inaugural Address. Both physicians are Honorary Presidents of the Association. Other members of the American Diabetes Association who have signified their intention of attending are Dr. Frank N. Allan, First Vice President, and Dr. George M. Guest, Councilor. Although the American Diabetes Association is not yet affiliated with the Federation, J. Richard Connelly, Executive Director, was designated by the Council at its January meeting to be the Association's official representative to the Congress.

Leyden is a historical city, situated in the center of Holland's beautiful flower-growing area. Plans are being made for several informal excursions to the surrounding countryside. The Congress will have its inaugural meeting, at which Dr. Best will speak, in the fine, old-world auditorium of the University of Leyden, founded in 1575. Scientific sessions and panel discussions will take place in Leyden's Academic Hospital, which has excellent facilities for meetings of this sort.

Arrangements have been made for physicians attending the Congress to stay at the well-known seaside resort hotel Noordwyk-on-the-Sea, on the North Sea Coast just eight miles from Leyden. Buses will transport the registrants between the hotel and the Congress meeting places.

Applications for reservations should be sent to Dr. F. Gerritzen, Secretary-Treasurer, International Diabetes Federation, 33 Prinsegracht, The Hague, Holland, before April 15, 1952. Further information about the Congress may be secured by writing Mr. Connelly at the Association's National Office. If feasible, further information about the program of the Congress will be included in the next issue of DIABETES.

THIRTY-THIRD ANNUAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

The 1952 Annual Session of the American College of Physicians will be held April 21 to 25, 1952, in the Public Auditorium, Cleveland, Ohio. Among the many papers, clinics and panel discussions listed in the Final Program, the following deal with diabetes:

Panel Discussion—Wednesday, April 23, 1952—MANAGEMENT OF DIABETES MELLITUS AND ITS COMPLICATIONS. Moderator: Garfield G. Duncan, Philadelphia. Panel members: Alexander Marble, Boston; Edward H. Mason, Montreal; E. Perry McCullagh, Cleveland; Thomas P. Sharkey, Dayton. Introduced by Robert W. Schneider, Cleveland.

Hospital Clinics—Thursday, April 24, 1952—USE OF N.P.H. IN DIABETES MELLITUS. M. Irving Sparks, at 9:15 a.m., St. Vincent Charity Hospital.

DIABETES. Garfield G. Duncan, Philadelphia, at 9:00 a.m., University Hospitals.

FRUCTOSE IN DIABETIC COMA. James W. Craig, at 9:20 a.m., University Hospitals.

Symposium on Diabetes—Friday, April 25, 1952—ENDOCRINE REGULATION OF THE BLOOD SUGAR. Jerome W. Conn, University of Michigan Medical School.

BASIC PRINCIPLES IN THE THERAPY OF DIABETES. Henry T. Ricketts, University of Chicago School of Medicine.

DIABETIC ACIDOSIS AS A THERAPEUTIC PROBLEM. Garfield G. Duncan, Jefferson Medical College of Philadelphia.

THE KIMMELSTIEL-WILSON SYNDROME. Stanton L. Eversole (by invitation), Johns Hopkins University School of Medicine.

DIABETIC RETINOPATHY. Bernard Becker (by invitation), Johns Hopkins University School of Medicine.

JOURNAL OF CLINICAL NUTRITION

The Nutritional Press has announced a new international bimonthly journal entitled the *Journal of Clinical Nutrition.* This new publication will be devoted to "the practical application of the newer knowledge of nutrition," and will feature original papers, review articles, and an integrated abstract section. S. O. Waife, M.D., of Philadelphia, is the Editor in Chief.

PERSONALS

Dr. Joseph H. Barach, Treasurer and Past President of the Association, has been appointed to succeed Dr. John A. Reed as a member of the National Advisory Arthritis and Metabolic Disease Council, Research Grants Division, U. S. Public Health Service. Dr. Barach has also been appointed a member of the Committee on Lipoproteins and Atherosclerosis, National Health Institutes, U.S. Public Health Service, and the Inter-Council Committee on Institutional Grants, Research Grants Division, U. S. Public Health Service.

Dr. Peter H. Forsham was recently appointed Associate Professor of Medicine and Pediatrics at the

University of California Medical School in San Francisco. Dr. Forsham was formerly at the Peter Brent Brigham Hospital in Boston.

The appointment of Dr. Henry B. Mulholland to the Executive Committee of the Commission on Chronic Illness has been announced. Dr. Mulholland is Acting Head of the Department of Internal Medicine and Assistant Dean of the University of Virginia Medical School, and Professor of Practice Medicine at that institution. He is also Chairman of the Committee on Scientific Exhibits, Chairman of the Subcommittee on Treatment of the Committee on Emergency Medical Care, and member of the Council of the American Diabetes Association.

OBITUARIES

LOUIS CHARLES ROSENBERG, M.D., who became a member of the American Diabetes Association in 1948, died November 3, 1951, in Newark, New Jersey, the city where he was born. Dr. Rosenberg was 60 years of age.

After obtaining his M.D. degree from George Washington University School of Medicine in 1916, Dr. Rosenberg began specializing in pediatrics, and in 1935 was certified by the American Board of Pediatrics. He was a fellow of the American Academy of Pediatrics, the American College of Physicians, and the American Medical Association, and member of the Association for the Study of Internal Secretions.

Dr. Rosenberg served as Attending Pediatrician at the Essex County Hospital for Contagious Diseases, as consultant at Babies Hospital-Coit Memorial in Newark, and as Senior Attending Pediatrician at Newark Beth Israel Hospital.

KATHARINE STRONG BIELBY, Associate Member of the American Diabetes Association, died on October 14, 1951, at the age of 63.

Miss Bielby was born August 29, 1887, at Kent, Connecticut, and received her M.S. from Teachers College at Columbia University, New York. After working for a time in Dr. Frederick Allen's Diabetic Hospital, and teaching in private schools for six years, Miss Bielby moved to Salt Lake City, where she joined the staff of Dr. Grove's Latter Day Saints Hospital as a dietitian. For many years she was Head Dietitian of this institution, and director of its Training School for Dietitians. For the past six years, she was Head Dietitian at the University Hospital at Syracuse, New York.

Among her affiliations, in addition to the American Diabetes Association, were The American Dietetic Association, the Western States Hospital Association, and the Utah State Nutrition Council.

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